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Dated 1 December 1998

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1/77

Request for grant of a patent

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28JAN98 E333560-1 [illegible] The Patent Offic
P01/7700 25.00 - 9801630.6 Cardiff Road
Newport
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1. Your reference — JBV/JR/P31957

2. Patent application number
(The Patent Office will fill in his part) — 26 JAN 1998 — 9801630.6

3. Full name, address and postcode of the or of each applicant *(underline all surnames)*

Patents ADP number *(if you know it)*

If the applicant is a corporate body, give the country/state of its incorporation

SMITHKLINE BEECHAM PLC
NEW HORIZONS COURT, BRENTFORD,
MIDDLESEX TW8 9EP

5800974002

UNITED KINGDOM

4. Title of the invention — Novel Compounds

5. Name of your agent *(if you have one)*

"Address for service" in the United Kingdom to which all correspondence should be sent
(including the postcode)

Patents ADP number *(if you know it)*

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TWO NEW HORIZONS COURT
BRENTFORD
MIDDLESEX TW8 9EP

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6. If you are declaring priority from one or more earlier patent applications, give the country and the date of filing of the or each of these earlier applications and *(if you know it)* the or each application number

Country	Priority application number *(if you know it)*	Date of filing *(day / month / year)*

7. If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application

Number of earlier application	Date of filing *(day / month / year)*

8. Is a statement of inventorship and of right to grant of a patent required in support of this request? *(Answer yes if:*
a) any applicant named in part 3 is not an inventor, or
b) there is an inventor who is named as an applicant, or
c) any named applicant is a corporate body
See note (d)

9. Enter the number of sheets for any of the following items you are filing with this form. Do not count copies of the same document

Continuation sheets of this form	
Description	59
Claim(s)	
Abstract	
Drawings	

10. If you are also filing any of the following, state how many against each item.

Priority Documents	
Translations of priority documents	
Statement of inventorship and right to grant of a patent *(Patents Form 1/77)*	
Request for preliminary examination and search *(Patents Form 9/77)*	
Request for substantive examination *(Patents Form 10/77)*	
Any other documents *(please specify)*	

11. We request the grant of a patent on the basis of this application

Signature _____ Date 26-Jan-98

J Valentine

12. Name and daytime telephone number of person to contact in the United Kingdom: J Valentine 01279 644401

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Medicaments

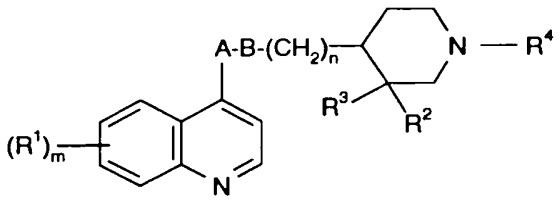
This invention relates to novel medicaments, being novel antibacterial compositions based upon a novel use of known quinoline compounds, as well as novel quinoline compounds.

DE 2315148A, EP 030044, NL7908030, EP0053964, EP0031753, EP0042781 and BE706646 disclose quinoline compounds having cardiovascular, hypnotic, anticonvulsant, and antimalerial effect.

EP0579263, EP0742207, JP2169569, EP0296560, WO9103243, EP0449186 disclose piperidine compounds as acetylcholinesterase inhibitors and sigma receptor antagonists

The present inventors have discovered that certain quinoline compounds have an unexpected antibacterial effect, which has lead to development of novel formulations incorporating such quinolines.

Accordingly this invention provides a method of treatment of bacterial infections in mammals, particularly in man, which method comprises the administration to a mammal in need of such treatment of an effective amount of a quinoline of formula (I) or a pharmaceutically acceptable derivative thereof:



(I)

wherein:

m is 1 or 2

each R^1 is independently hydroxy; (C_{1-6}) alkoxy optionally substituted by (C_{1-6})alkoxy, amino optionally substituted by one or two (C_{1-6})alkyl, acyl or (C_{1-6})alkylsulphonyl groups, NH_2CO, hydroxy, thiol, (C_{1-6})alkylthio, heterocyclylthio, heterocyclyloxy, arylthio, aryloxy, acylthio, acyloxy or (C_{1-6})alkylsulphonyloxy; (C_{1-6})alkoxy-substituted (C_{1-6})alkyl; halogen; (C_{1-6})alkyl; (C_{1-6})alkylthio; trifluoromethyl; nitro; azido; acyl; acyloxy; acylthio; (C_{1-6})alkylsulphonyl; (C_{1-6})alkylsulphoxide; arylsulphonyl; arylsulphoxide or an amino group optionally substituted by one or two (C_{1-6})alkyl, acyl or (C_{1-6})alkylsulphonyl groups;

either R^2 is hydrogen; and

R^3 is hydrogen or (C_{1-6})alkyl or (C_{2-6})alkenyl optionally substituted with 1 to 3 groups selected from:

thiol; halogen; (C_{1-6})alkylthio; trifluoromethyl; azido; (C_{1-6})alkoxycarbonyl; (C_{1-6})alkylcarbonyl; (C_{2-6})alkenyloxycarbonyl; (C_{2-6})alkenylcarbonyl; hydroxy optionally substituted by (C_{1-6})alkyl, (C_{2-6})alkenyl, (C_{1-6})alkoxycarbonyl, (C_{1-6})alkylcarbonyl, (C_{2-6})alkenyloxycarbonyl, (C_{2-6})alkenylcarbonyl or aminocarbonyl wherein the amino group is optionally substituted by (C_{1-6})alkyl, (C_{2-6})alkenyl, (C_{1-6})alkylcarbonyl or (C_{2-6})alkenylcarbonyl; amino optionally mono- or disubstituted by (C_{1-6})alkoxycarbonyl, (C_{1-6})alkylcarbonyl, (C_{2-6})alkenyloxycarbonyl, (C_{2-6})alkenylcarbonyl, (C_{1-6})alkyl, (C_{2-6})alkenyl, (C_{1-6})alkylsulphonyl, (C_{2-6})alkenylsulphonyl or aminocarbonyl wherein the amino group is optionally substituted by (C_{1-6})alkyl or (C_{2-6})alkenyl; aminocarbonyl wherein the amino group is optionally mono- or disubstituted by (C_{1-6})alkyl, (C_{2-6})alkenyl, (C_{1-6})alkoxycarbonyl, (C_{1-6})alkylcarbonyl, (C_{2-6})alkenyloxycarbonyl or (C_{2-6})alkenylcarbonyl]; oxo; (C_{1-6})alkylsulphonyl; (C_{2-6})alkenylsulphonyl; or (C_{1-6})aminosulphonyl wherein the amino group is optionally substituted by (C_{1-6})alkyl or (C_{2-6})alkenyl; or

R^2 and R^3 together are a divalent residue $=CR^5R^6$ where R^5 and R^6 are independently selected from H, (C_{1-6})alkyl, (C_{2-6})alkenyl, aryl(C_{1-6})alkyl and aryl(C_{2-6})alkenyl, any alkyl or alkenyl moiety being optionally substituted by 1 to 3 groups selected from those listed above for substituents on R^3;

R^4 is a group $-CH_2-R^5$ in which R^5 is selected from:

(C_{1-12})alkyl; hydroxy(C_{1-12})alkyl; (C_{1-12})alkoxy(C_{1-12})alkyl; (C_{1-12})alkanoyloxy(C_{1-12})alkyl; (C_{3-6})cycloalkyl; hydroxy(C_{3-6})cycloalkyl; (C_{1-12})alkoxy(C_{3-6})cycloalkyl; (C_{1-12})alkanoyloxy(C_{3-6})cycloalkyl; (C_{3-6})cycloalkyl(C_{1-12})alkyl; hydroxy-, (C_{1-12})alkoxy- or (C_{1-12})alkanoyloxy-(C_{3-6})cycloalkyl(C_{1-12})alkyl; cyano; cyano(C_{1-12})alkyl; (C_{2-12})alkenyl; (C_{2-12})alkynyl; tetrahydrofuryl; mono- or di-(C_{1-12})alkylamino(C_{1-12})alkyl; acylamino(C_{1-12})alkyl; (C_{1-12})alkyl- or acyl-aminocarbonyl(C_{1-12})alkyl; mono- or di- (C_{1-12})alkylamino(hydroxy) (C_{1-12})alkyl; optionally substituted phenyl(C_{1-12})alkyl, phenoxy(C_{1-12})alkyl or phenyl(hydroxy)(C_{1-12})alkyl; optionally substituted diphenyl(C_{1-12})alkyl; optionally substituted phenyl(C_{2-12})alkenyl; optionally substituted benzoyl or benzoyl(C_{1-12})alkyl; optionally substituted heteroaryl or heteroaryl(C_{1-12})alkyl;and optionally substituted heteroaroyl or heteroaroyl(C_{1-12})alkyl;

n is 0, 1 or 2;

A is NR^{11}, O, $S(O)_x$ or CR^6R^7 and B is NR^{11}, O, $S(O)_x$ or CR^8R^9 where x is 0, 1 or 2 and wherein:

each of R^6 and R^7 R^8 and R^9 is independently selected from: H; thiol; (C_{1-6})alkylthio; halo; trifluoromethyl; azido; (C_{1-6})alkyl; (C_{2-6})alkenyl; (C_{1-6})alkoxycarbonyl; (C_{1-6})alkylcarbonyl; (C_{2-6})alkenyloxycarbonyl; (C_{2-6})alkenylcarbonyl; hydroxy, amino or aminocarbonyl optionally substituted as for corresponding substituents in R^3; (C_{1-6})alkylsulphonyl; (C_{2-6})alkenylsulphonyl; or (C_{1-6})aminosulphonyl wherein the amino group is optionally substituted by (C_{1-6})alkyl or (C_{1-6})alkenyl;

or R^6 and R^8 together represent a bond and R^7 and R^9 are as above defined;

or R^6 and R^7 or R^8 and R^9 together represent oxo;

and each R^{11} is independently H, trifluoromethyl, (C_{1-6})alkyl, (C_{1-6})alkenyl, (C_{1-6})alkoxycarbonyl, (C_{1-6})alkylcarbonyl, aminocarbonyl wherein the amino group is optionally mono- or di-substituted by (C_{1-6})alkoxycarbonyl, (C_{1-6})alkylcarbonyl, (C_{1-6})alkenyloxycarbonyl, (C_{2-6})alkenylcarbonyl, (C_{1-6})alkyl or (C_{1-6})alkenyl;

provided that A and B cannot both be selected from NR^{11}, O and $S(O)_x$ and when one of A and B is CO the other is not CO, O or $S(O)_x$.

The invention also provides the use of a compound of formula (I) or a pharmaceutically acceptable derivative thereof in the manufacture of a medicament for use in the treatment of bacterial infections in mammals.

The invention also provides a pharmaceutical composition for use in the treatment of bacterial infections in mammals comprising a compound of formula (I), or a pharmaceutically acceptable derivative thereof, and a pharmaceutically acceptable carrier.

In a preferred aspect, when A is CH_2 or CHOH and B is CH_2 and n is 1 the substitutents at the 3- and 4-position of the piperidine ring are cis.

When R^1 is substituted alkoxy it is preferably substitituted by optionally substituted amino, more preferably by amino. Suitable examples of R^1 alkoxy include methoxy, n-propyloxy, i-butyloxy, pentyloxy, aminopentyloxy, phthalimido pentyloxy or 2-aminocarbonylprop-2-oxy. Preferably R^1 is in the 6-position on the quinoline nucleus. Preferably R^1 is methoxy or amino(C_{3-5})alkyloxy.

Preferably m is 1.

R^3 is preferably (C_{1-6}) alkyl, (C_{1-6}) alkenyl, optionally substituted hydroxy-(C_{1-6}) alkyl or, more preferably 1,2-dihydroxy(C_{2-6})alkyl wherein the 2-hydroxy group is optionally substituted Preferred examples of R^3 include 1- or 2-hydroxyethyl, 2- or 3-hydroxypropyl or 1,2-dihydroxyethyl wherein the optional hydroxy group substitutent is

alkylcarbonyl or aminocarbonyl where the amino group is optionally substituted. Other suitable examples of R^3 include ethyl or vinyl.

When R^2 and R^3 together form a group, this is preferably $=CHCH_3$.

Preferably A is NH, O, CH_2, CHOH, $CH(NH_2)$, C(Me)(OH) or CH(Me).

Preferably B is CH_2, CO or S.

Preferably n is 0 or 1.

More preferably:

when A is NH, B is CO and n is 1 or 0;

when A is O, B is CH_2 and n is 1 or 0;

when A is CH_2 or CH_2OH, B is CH_2, and n is 1 or 0;

when A is $CH(NH_2)$, C(Me)(OH) or CH(Me), B is CH_2 and n is 1.

Suitable groups R^4 include n-pentyl, n-hexyl, n-heptyl, n-octyl, n-nonyl, n-decyl, n-dodecyl, methoxybutyl, phenylethyl, phenylpropyl or 3-phenyl-prop-2-en-yl optionally substituted on the phenyl ring, 3-benzoylpropyl, 4-benzoylbutyl, 3-pyridylmethyl, 3-(4-fluorobenzoyl)propyl, cyclohexylmethyl, cyclobutylmethyl, t-butoxycarbonylaminomethyl and phenoxyethyl.

Preferably R^4 is (C_{5-10})alkyl, phenyl(C_{2-4})alkyl or phenyl(C_{3-4})alkenyl, optionally substituted on the phenyl ring, more preferably hexyl, heptyl , 3-phenyl-prop-2-en-yl or 3-phenylpropyl.

A suitable substituent on the phenyl rings in R^4 is fluorine or ethyl, for example in a para-position relative to the link to the nucleus.

Halo or halogen includes fluoro, chloro, bromo and iodo.

The term 'heterocyclic' as used herein includes aromatic and non-aromatic, single and fused, rings suitably containing up to four hetero-atoms in each ring selected from oxygen, nitrogen and sulphur, which rings may be unsubstituted or substituted by, for example, up to three groups selected from optionally substituted amino, halogen, (C_{1-6})alkyl, (C_{1-6})alkoxy, halo(C_{1-6})alkyl, hydroxy, carboxy, carboxy salts, carboxy esters such as (C_{1-6})alkoxycarbonyl, (C_{1-6})alkoxycarbonyl(C_{1-6})alkyl, aryl, and oxo groups. Each heterocyclic ring suitably has from 4 to 7, preferably 5 or 6, ring atoms. A fused heterocyclic ring system may include carbocyclic rings and need include only one heterocyclic ring. Compounds within the invention containing a heterocyclyl group may occur in two or more tautometric forms depending on the nature of the heterocyclyl group; all such tautomeric forms are included within the scope of the invention.

Where an amino group forms part of a single or fused non-aromatic heterocyclic ring as defined above suitable optional substituents in such substituted amino groups include (C_{1-6})alkyl optionally substituted by hydroxy, (C_{1-6})alkoxy, thiol, (C_{1-6})alkylthio, halo or trifluoromethyl, and amino-protecting groups such as acyl or (C_{1-6})alkylsulphonyl groups.

The term 'heteroaryl' includes the aromatic heterocyclic groups referred to above. Examples of heteroaryl groups include pyridyl, triazolyl, tetrazolyl, indolyl, thienyl, isoimidazolyl, thiazolyl, furanyl,quinolinyl, imidazolidinyl and benzothienyl.

When used herein the term 'aryl', includes phenyl and naphthyl, each optionally substituted with up to five, preferably up to three, groups selected from halogen, mercapto, (C_{1-6})alkyl, phenyl, (C_{1-6})alkoxy, hydroxy(C_{1-6})alkyl, mercapto (C_{1-6})alkyl, halo(C_{1-6})alkyl, hydroxy, optionally substituted amino, nitro, carboxy, (C_{1-6})alkylcarbonyloxy, (C_{1-6})alkoxycarbonyl, formyl, or (C_{1-6})alkylcarbonyl groups.

The term 'acyl' includes (C_{1-6})alkoxycarbonyl, formyl or (C_{1-6}) alkylcarbonyl group.

Compounds of formula (I) wherein:
R^3 is hydroxy(C_{1-6})alkyl or 1,2-dihydroxy(C_{2-6})alkyl optionally substituted on the hydroxy group(s) as claimed, hereinafter 'compounds of formula (IA)', are novel and as such form part of the invention.

The invention also provides a pharmaceutical composition comprising a compound of formula (IA), or a pharmaceutically acceptable derivative thereof, and a pharmaceutically acceptable carrier.

Some of the compounds of this invention may be crystallised or recrystallised from solvents such as organic solvents. In such cases solvates may be formed. This invention includes within its scope stoichiometric solvates including hydrates as well as compounds containing variable amounts of water that may be produced by processes such as lyophilisation.

Since the compounds of formula (I) are intended for use in pharmaceutical compositions it will readily be understood that they are each provided in substantially pure form, for example at least 60% pure, more suitably at least 75% pure and preferably at least 85%, especially at least 98% pure (% are on a weight for weight basis). Impure preparations of the compounds may be used for preparing the more pure forms used in the pharmaceutical compositions; these less pure preparations of the compounds should contain at least 1%, more suitably at least 5% and preferably from 10 to 59% of a compound of the formula (I) or salt thereof.

Pharmaceutically acceptable derivatives of the above-mentioned compounds of formula (I) include the free base form or their acid addition or quaternary ammonium salts, for example their salts with mineral acids e.g. hydrochloric, hydrobromic or sulphuric acids, or organic acids, e.g. acetic, fumaric or tartaric acids. Compounds of formula (I) may also be prepared as the N-oxide.

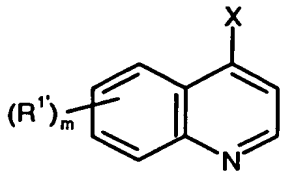
Certain of the above-mentioned compounds of formula (I) may exist in the form of optical isomers, e.g. diastereoisomers and mixtures of isomers in all ratios, e.g. racemic mixtures. The invention includes all such forms, in particular the pure isomeric forms. For

examples the invention includes compound in which an A-B group $CH(OH)-CH_2$ is in either isomeric configuration.

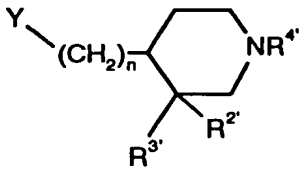
Compounds of formula (I) may be prepared by the processes described and exemplified in the above-mentioned patent publications.

In a further aspect of the invention there is provided a process for preparing novel compounds of formula (I), or a pharmaceutically acceptable derivative thereof, which process comprises:

(a) reacting a compound of formula (IV) with a compound of formula (V):



(IV)



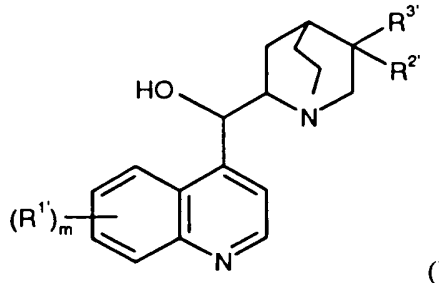
(V)

wherein m, n, R^1, R^2, R^3 and R^4 are as defined in formula (I), and X and Y may be the following combinations:

(i) X is M and Y is $CH_2CO_2R^x$
(ii) X is CO_2R^y and Y is $CH_2CO_2R^x$
(iii) one of X and Y is $CH=SPh_2$ and the other is CHO
(iv) X is CH_3 and Y is CHO
(v) X is CH_3 and Y is CO_2R^x
(vi) X is $CH_2CO_2R^y$ and Y is CO_2R^x
(vii) X is $CH=PR^z{}_3$ and Y is CHO
(viii) X is CHO and Y is $CH=PR^z{}_3$
(ix) X is halogen and Y is $CH=CH_2$
(x) one of X and Y is COW and the other is $NHR^{11'}$ or NCO
(xi) one of X and Y is $(CH_2)_p$-V and the other is $(CH_2)_qNHR^{11'}$, $(CH_2)_qOH$, $(CH_2)_qSH$ or $(CH_2)_qSCOR^x$ where p+q=1
(xii) one of X and Y is CHO and the other is $NHR^{11'}$
(xiii) one of X and Y is OH and the other is $-CH=N_2$

in which V and W are leaving groups, R^x and R^y are (C_{1-6})alkyl and R^z is aryl or (C_{1-6})alkyl;

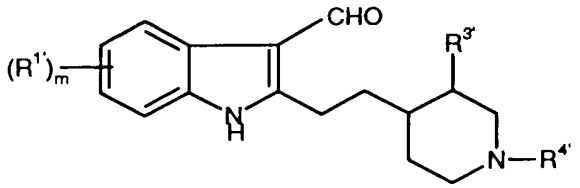
(b) rearranging a compound of formula (II):



(II)

to give a compound of formula (III) which is a compound of formula (I) where n is 1, A-B is $COCH_2$ and R^2 is H, or a compound of formula (VII) which is a compound of formula (I) where n is 1, A-B is $CHOHCH_2$ or CH_2CHOH and R^2 is H;

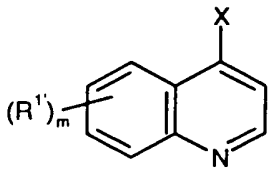
(c) photooxygenating a compound of formula (VI):



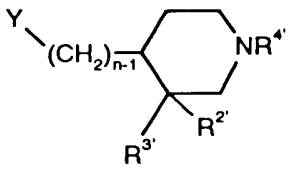
(VI)

or

(d) reacting a compound of formula (IV) with a compound of formula (Vb):



(IV)



(Vb)

wherein m, n, R^1, R^2, R^3 and R^4 are as defined in formula (I), X is $CH_2NHR^{11'}$ and Y is CHO or COW or X is CH_2OH and Y is $-CH=N_2$;

in which $R^{11'}$, $R^{1'}$, $R^{2'}$, $R^{3'}$ and $R^{4'}$ are R^{11}, R^1, R^2, R^3 and R^4 or groups convertible thereto, and thereafter optionally or as necessary converting $R^{11'}$, $R^{1'}$, $R^{2'}$, $R^{3'}$ and $R^{4'}$ to $R^{11'}$, R^1, R^2, R^3 and R^4, converting A-B to other A-B, interconverting R^{11}, R^1, R^2, R^3 and/or R^4 and forming a pharmaceutically acceptable derivative thereof.

Process variants (a)(i), (a)(ii), (b) in certain aspects and (c) initially produce compounds of formula (I) where A-B is $COCH_2$. The product of variants (b) and (c) have n=1.

Process variants (a)(iii) and (b) in other aspects initially produce compounds of formula (I) wherein A-B is CH_2CHOH or $CHOHCH_2$.

Process variant (a)(iv) initially produces compounds of formula (I) wherein A-B is CH_2CHOH. .

Process variants (a)(v) and (a)(vi), initially produce compounds of formula (I) wherein A-B is CH_2CO.

Process variants (a)(vii), (a)(viii) and (a)(ix) initially produce compounds where A-B is CH=CH.

Process variant (a)(x) initially produces compounds of formula (I) wherein A-B is $CONHR^{11}$ or $NHR^{11}CO$.

Process variant (a)(xi) initially produces compounds of formula (I) wherein one of A and B is CH_2 and the other is NHR^{11}, O or S.

Process variant (a)(xii), initially produce compounds of formula (I) wherein A-B is CH_2NHR^{11} or $NHR^{11}CH_2$.

Process variant (a)(xiii) initially produces compounds of formul a(I) wherein A-B is OCH_2 or CH_2O.

Process variant (d) initially produces compounds of formula (I) wherein Al is CH_2 and B is NHR^{11} or O.

In process variant (a)(i) M is preferably an alkali metal, more preferably Li. The reaction is conducted in an aprotic solvent preferably THF, ether or benzene at -78 to 25°C. An analogous route is described in G. Grethe et al (1972) Helv. Chimica.Acta., 55, 1044.

In process variant (a)(ii) the process is two step: firstly a condensation using a base, preferably sodium hydride or alkoxide, sodamide, alkyl lithium or lithium dialkylamide, preferably in an aprotic solvent e.g. ether, THF or benzene; secondly, hydrolysis using an inorganic acid, preferably HCl in aqueous organic solvent at 0-100°C. Analogous routes are described in DE330945, EP31753, EP53964 and H. Sargent, J. Am. Chem. Soc. **68**, 2688-2692 (1946).

In process variant (a)(iii) if a base is used it is preferably NaH, KH, an alkyl lithium e.g. BuLi, a metal alkoxide e.g. NaOEt, sodamide or lithium dialkylamide e.g.di-isopropylamide. An analogous method is described in US 3989691 and in Taylor et al. (1972) JACS 94, 6218)

In process variant (a)(iv) the reaction is carried out in the presence of a base, preferably organometallic or metal hydride e.g. NaH, lithium diisopropylamide or NaOEt,

preferably in an aprotic solvent, preferably THF, ether or benzene at -78 to 25°C (analogous process in Gutswiller et al. (1978) JACS 100, 576).

In process variant (a)(v) the reaction is carried out in the presence of a base, preferably organometallic or metal hydride e.g. NaH, lithium diisopropylamide or NaOEt, preferably in an aprotic solvent, preferably THF, ether or benzene at -78 to 25°C. An analogous method is described in US 3772302.

In process variant (a)(vi) a similar Claisen methodology to that described for (a)(ii) is used, analogous to that described in Soszko et. al., Pr.Kom.Mat. Przyr.Poznan.Tow.Przyj.Nauk., (1962), 10, 15.

In process variants (a)(vii) and (viii) if a base is used it is preferably NaH, KH, an alkyl lithium e.g. BuLi, a metal alkoxide e.g. NaOEt, sodamide or lithium dialkylamide e.g.di- isopropylamide. An analogous method is described in US 3989691 and M.Gates et. al. (1970) J. Amer.Chem.Soc., 92, 205, as well as Taylor et al. (1972) JACS 94, 6218.

In process variant (a)(ix) the reaction is carried out using palladium catalysis. The palladium catalyst is preferably palladium acetate in the presence of trialkyl or triaryl phosphine and a trialkylamine e.g. triphenyl phosphine and tributylamine. An analogous method is described in S. Adam et. al. (1994) Tetrahedron, 50, 3327.

In process variant (a)(x), or (d) where Y is COW,the reaction is a standard amide formation reaction:

1. Activation of a carboxylic acid (e.g., to an acid chloride, mixed anhydride, active ester, O-acyl-isourea or other species), and treatment with an amine (Ogliaruso, M. A.; Wolfe, J. F. in *The Chemistry of Functional Groups (Ed. Patai, S.) Suppl. B: The Chemistry of Acid Derivatives, Pt. 1* (John Wiley and Sons, 1979), pp 442-8; Beckwith, A. L. J. in *The Chemistry of Functional Groups (Ed. Patai, S.) Suppl. B: The Chemistry of Amides (Ed. Zabricky, J.)* (John Wiley and Sons, 1970), p 73 ff. The acid and amide are preferably reacted in the presence of an activating agent such as 1-(dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC) or 1-hydroxybenzotriazole (HOBT),

2. Aminolysis of esters (Suzuki, K.; Nagasawa, T. in *Encyclopedia of Reagents for Organic Synthesis (Ed. Paquette, L. A.)* (John Wiley and Sons, 1995), p 5188 and refs. cited therein.)

3. The specific methods of:

a. *in situ* conversion of an acid into the amine component by a modified Curtius reaction procedure (Shioiri, T.; Murata, M.; Hamada, Y., *Chem. Pharm. Bull.* **1987**, *35*, 2698)

b. *in situ* conversion of the acid component into the acid chloride under neutral conditions (Villeneuve, G. B.; Chan, T. H., *Tet. Lett.* **1997**, *38*, 6489).

In process variant (d) a final reduction step provides the required amine.

In process variant (a)(xi) where one of X and Y contains NHR^{11} the leaving group V is halogen and the reaction is a standard amine formation reaction such as direct alkylation described in (Malpass, J. R., in *Comprehensive Organic Chemistry,* Vol. 2 (Ed. Sutherland, I. O.), p 4 ff.) or aromatic nucleophilic displacement reactions (see references cited in *Comprehensive Organic Chemistry,* Vol. 6, p 946-947 (reaction index); Smith, D. M. in *Comprehensive Organic Chemistry,* Vol. 4 (Ed. Sammes, P. G.) p 20 ff.). This is analogous to the methods described in GB 1177849.

In process variant (a)(xi) where one of X and Y contains OH or SH, this is preferably converted to an OM or SM group where M is an alkali metal by treatment of an alcohol, thiol or thioacetate with a base. The base is preferably inorganic such as NaH, lithium diisopropylamide or sodium, or, for SH, metal alkoxide such as sodium methoxide. The X/Y group containing the thioacetate $SCOR^X$ is prepared by treatment of an alcohol or alkyl halide with thioacetic acid or a salt thereof under Mitsunobu conditions. The leaving group V is a halogen. The reaction may be carried out as described in Chapman et.al., J. Chem Soc., (1956),1563, Gilligan et. al., J. Med. Chem., (1992), **35**, 4344, Aloup et. al., J. Med. Chem. (1987), **30**, 24, Gilman et al., J.A.C.S. (1949), **71**, 3667 and Clinton et al., J.A.C.S. (1948), **70**, 491, Barluenga et al., J. Org. Chem. (1987) **52**, 5190. Alternatively where X is OH and Y is CH_2V, V is a hydroxy group activated under Mitsunobu conditions (Fletcher et.al. J Chem Soc. (1995), 623).

In process variants (a)(xii) and (d) where Y is CHO the reaction is a standard reductive alkylation using, e.g., sodium triacetoxyborohydride (Gribble, G. W. in *Encyclopedia of Reagents for Organic Synthesis (Ed. Paquette, L. A.)* (John Wiley and Sons, 1995), p 4649).

In process variant (a)(xiii), or (d) where X is CH_2OH and Y is $-CH=N_2$, the reaction is as described in den Hertzog et. al., recl.Trav. Chim. Pays-Bas, (1950),**69**, 700.

In process variant (b) the rearrangement may be effected by treatment with an acid, preferably an organic acid such as acetic acid and the reaction temperature is 80-120°C. Alternatively the compound of formula (II) is quaternised by treatment with an alkylating agent and treated with base such as KOH to give, depending upon the stereochemistry of the OH and the nature of the quaternery salt and base, either the ketone of formula (III) or an epoxide which can be opened to the alcohol of formula (VII by reduction (see EP0035821).

In process variant (c) the reaction is preferably carries out in an alcohol, preferably methanol under irradiation conditions which are known to generate singlet oxygen as described in M. Ihara et.al. (1988), J.Chem Soc Perkin Trans. 1, 1277.

Reduction of A or B CO to CHOH can be readily accomplished using reducing agents well known to those skilled in the art, e.g. sodium borohydride in aqueous ethanol

or lithium aluminiun hydride in ethereal solution.. This is analogous to methods described in EP 53964, US 384556 and J. Gutzwiller et. al. (1978) J.Amer.Chem.Soc., 100, 576.

The carbonyl group A or B may be reduced to CH_2 by treatment with a reducing agent such as hydrazine in ethylene glycol at 130-160°C in the presence of potassium hydroxide.

Reaction of a carbonyl group A or B with an organometallic reagent yields a group where R^6 or R^8 is OH and R^7 or R^9 is alkyl.

A hydroxy group A or B may be oxidised to a carbonyl group by oxidants well known to those skilled in the art , for example, manganese dioxide, pyridinium chlorochromate or pyridinium dichromate.

An A-B group $COCH_2$ may be converted to COCH-halogen, by treating the ketone or a derivative with a halogenating agent, reduced to CHOHCHCl and then converted via the epoxide to CH_2CHOH.

Methods for conversion of CH=CH by reduction to CH_2CH_2 are well known to those skilled in the art, for example using hydrogenation over palladium on carbon as catalyst. Methods for conversion of CH=CH to give the A-B group as $CHOHCH_2$ or CH_2CHOH are well known to those skilled in the art for example by epoxidation and subsequenct reduction by metal hydrides, hydration, hydroboration or oxymercuration.

A hydroxyalkyl group A-B CH_2CHOH or $CHOHCH_2$ may be dehydrated to give the group CH=CH by treatment with an acid anhydride such as acetic anhydride.

An amide group $CONHR^{11'}$ or $NHR^{11'}CO$ may be reduced to the amine using a reducing agent such as lithium aluminium hydride

A ketone group may be converted to an amide CONH via the oxime by a Beckmann rearrangement (Ogliaruso, M.A.; Wolfe, J. F., *ibid.* pp 450-451; Beckwith, A. L. J., *ibid.* pp 131 ff.)

A hydroxy group A or B may be converted to azido by activation and displacement e.g. under Mitsunobu conditions using hydrazoic acid or by treatment with diphenylphosphorylazide and base, and the azido group in turn may be reduced to amino by hydrogenation.

A sulphur group A or B may be converted to the sulphoxide $S(O)_x$ by oxidation with peracids or a wide range of oxidants known to those skilled in the art (see Advanced Organic Chemistry *(Ed. March, J.)* (John Wiley and Sons, 1985), p 1089 and refs. cited therein).

$R^{1'}$, $R^{2'}$, $R^{3'}$ and $R^{4'}$ are preferably R^1, R^2, R^3 and R^4. $R^{1'}$ is preferably methoxy. $R^{2'}$ is preferably hydrogen. $R^{3'}$ is preferably vinyl. $R^{4'}$ is preferably H.

Conversions of $R^{1'}$, $R^{2'}$, $R^{3'}$ and $R^{4'}$ and interconversions of R^1, R^2, R^3 and R^4 are conventional. In compounds which contain an optionally substituted hydroxy group,

suitable conventional hydroxy protecting groups which may be removed without disrupting the remainder of the molecule include acyl and alkylsilyl groups.

For example $R^{1'}$ methoxy is convertible to $R^{1'}$ hydroxy by treatment with lithium and diphenylphosphine (general method described in Ireland et. al. (1973) J.Amer.Chem.Soc.,7829) or HBr.

$R^{3'}$ alkenyl is convertible to hydroxyalkyl by hydroboration using a suitable reagent such as 9-borabicyclo[3.3.1]nonane, epoxidation and reduction or oxymercuration.

R^3 1,2-dihydroxy can be prepared from $R^{3'}$ alkenyl using osmium tetroxide or other reagents well known to those skilled in the art (see Advanced Organic Chemistry *(Ed. March, J.)* (John Wiley and Sons, 1985), p 732-737 and refs. cited therein) or epoxidation followed by hydrolysis (see Advanced Organic Chemistry *(Ed. March, J.)* (John Wiley and Sons, 1985), p 332,333 and refs. cited therein).

R^3 vinyl can be chain extended by standard homologation e.g by conversion to hydroxyethyl followed by oxidation to the aldehyde which is then subjected to a Wittig reaction.

Compounds of formula (I) where R^2 and R^3 are a divalent residue $=CR^5R^6$ can be prepared by treatment of a compound of formula (I) where R^3 is alken-1-yl with a strong base in an aprotic solvent. Suitable bases include $Ph_2PLi/PhLi$ (as described in Ireland et. al., J. Amer. Chem .Soc. (1973), 7829), t-BuLi, and suitable solvents include THF and ether.

Substituents on R^3 alkyl or alkenyl may be interconverted by conventional methods, for example hydroxy may be derivatised by esterification, acylation or etherification. Hydroxy groups may be converted to halogen, thiol, alkylthio, azido, alkylcarbonyl, amino, aminocarbonyl, oxo, alkylsulphonyl, alkenylsulphonyl or aminosulphonyl by conversion to a leaving group and substitution by the required group or oxidation as appropriate or reaction with an activated acid, isocyanate or alkoxyisocyanate.

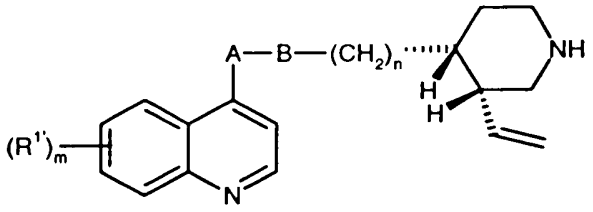
In a further aspect the invention provides a process for the preparation of a compound of formula (IA) or a pharmaceutically acceptable derivative thereof which comprises converting a compound of formula (I) in which R^3 is alkenyl in to a compound of formula (IA) and forming a pharmaceutically acceptable derivative thereof.

NH is converted to NR^4 by conventional means such as alkylation with an alkyl halide in the presence of base, acylation/reduction or reductive alkylation with an aldehyde.

It will be appreciated that under certain circumstances interconvertions may interfere, for example, A or B hydroxy groups and the piperidine NH will require protection e.g. as a carboxy- or silyl-ester group for hydroxy and as an acyl derivative for piperidine nitrogen, during conversion of $R^{1'}$, $R^{2'}$, $R^{3'}$ or $R^{4'}$.

Examples containing a *trans*-3,4-substituted piperidine ring may be prepared from the trans-3-vinyl-4-substituted piperidine prepared from the corresponding 3-vinyl-4-*cis*-isomer by the method of G. Engler *et al.* Helv. Chim. Acta **68**, 789-800 (1985); also described in Patent Application EP 0031753 (Pharmindustrie).

The method involves heating a 3-vinyl-4-alkyl-piperidine derivative of formula (VIII):



(VIII)

(prepared as an intermediate in the process of the invention) in dilute acid, preferably hydrochloric acid at pH 3.5, with 0.3-1.0 mol equivalents of formaldehyde. The main product of the reaction is the *trans*-isomer, which may be separated from the small quantity of *cis* isomer present, by conventional silica gel chromatography. It is convenient to convert the mixture of cis- and *trans*-piperidines ($R^{4'}$ = H) to the tertiary amines of formula (I) by alkylation with an alkyl halide (preferably an iodide) in DMF in the presence of anhydrous potassium carbonate, prior to silica gel chromatography.

Compounds of formula (II) include quinine and derivatives thereof.

Compounds of formulae (IV) and (V) are known compounds or prepared analogously, see for example the references cited above for reaction variant (a).

For compounds of formula (V) where Y is $NHR^{11'}$ suitable amines may be prepared from the corresponding acid or alcohol (Y is CO_2H or CH_2OH). In a first instance, an N-protected piperidine containing an acid bearing substituent, can undergo a Curtius rearrangement and the intermediate isocyanate can be converted to a carbamate by reaction with an alcohol. Conversion to the amine may be achieved by standard methods well known to those skilled in the art used for amine protecting group removal. For example, the t-butoxycarbonyl-protected 3-vinyl-4-piperidine acetic acid can undergo a Curtius rearrangement e.g. on treatment with diphenylphosphoryl azide and heating, and the intermediate isocyanate reacts in the presence of 2-trimethylsilylethanol to give the trimethylsilylethylcarbamate (T.L.Capson & C.D.Poulter, Tetrahedron Letters, 1984, 25, 3515). This undergoes cleavage on treatment with tetrabutylammonium fluoride to give the 4-piperidinemethylamine.

In a second instance, an N-protected piperidine containing an alcohol bearing substituent undergoes a Mitsunobu reaction (for example as reviewed in Mitsunobu, Synthesis, (1981), 1), for example with succinimide in the presence of diethyl azodicarboxylate and triphenylphosphine to give the phthalimidoethylpiperidine.

Removal of the phthaloyl group, for example by treatment with methylhydrazine, gives the amine of formula (V).

Compounds of formula (VI) are known compounds or may be prepared analogously, see for example Ihara et al JCS Perkin 1 1988, 1277-1281.

Conversions of $R^{1'}$, $R^{2'}$ and $R^{3'}$ may be carried out on the intermediates of formulae (II), (III), (IV), (V) and (VI) prior to their reaction to produce compounds of formula (I) in the same way as described above for conversions after their reaction.

For example, a compound of formula (II) where $R^{3'}$ is an alken-1-yl group can be isomerised to a compound where $R^{2'}$ and $R^{3'}$ together are a divalent residue $=CR^5R^6$ with acids such as HBr by methods analogous to that described in Diaz-Arauzo et. al. J. Natural Products, (1990), **53**, 112, and then treated with subsequent conversion to compounds of formula (III) as described inRenfrew and Butler, J. Amer. Chem.Soc., (1940), **62**, 3304.

Diaz-Arauzo et. al. J. Natural Products, (1990), **53**, 112, describe preparation of compounds where $R^{3'}$ in compounds of formula (II) is 1,2-dihydroxyethyl from $R^{3'}$ is vinyl using osmium tetroxide.

Where a *trans*-substituted compound of formula (I) is required, a *trans*-substituted piperidine moiety of formula (V) may be prepared from the corresponding *cis* isomer of formula (V) by heating in formaldehyde with a substituent that can subsequently be converted to the required group $(CH_2)_nY$, for example CH_2CO_2R (where R is an alkyl group eg methyl or ethyl).

The pharmaceutical compositions of the invention include those in a form adapted for oral, topical or parenteral use and may be used for the treatment of bacterial infection in mammals including humans.

The antibiotic compounds according to the invention may be formulated for administration in any convenient way for use in human or veterinary medicine, by analogy with other antibiotics.

The composition may be formulated for administration by any route, such as oral, topical or parenteral. The compositions may be in the form of tablets, capsules, powders, granules, lozenges, creams or liquid preparations, such as oral or sterile parenteral solutions or suspensions.

The topical formulations of the present invention may be presented as, for instance, ointments, creams or lotions, eye ointments and eye or ear drops, impregnated dressings and aerosols, and may contain appropriate conventional additives such as preservatives, solvents to assist drug penetration and emollients in ointments and creams.

The formulations may also contain compatible conventional carriers, such as cream or ointment bases and ethanol or oleyl alcohol for lotions. Such carriers may be present as

from about 1% up to about 98% of the formulation. More usually they will form up to about 80% of the formulation.

Tablets and capsules for oral administration may be in unit dose presentation form, and may contain conventional excipients such as binding agents, for example syrup, acacia, gelatin, sorbitol, tragacanth, or polyvinylpyrollidone; fillers, for example lactose, sugar, maize-starch, calcium phosphate, sorbitol or glycine; tabletting lubricants, for example magnesium stearate, talc, polyethylene glycol or silica; disintegrants, for example potato starch; or acceptable wetting agents such as sodium lauryl sulphate. The tablets may be coated according to methods well known in normal pharmaceutical practice. Oral liquid preparations may be in the form of, for example, aqueous or oily suspensions, solutions, emulsions, syrups or elixirs, or may be presented as a dry product for reconstitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives, such as suspending agents, for example sorbitol, methyl cellulose, glucose syrup, gelatin, hydroxyethyl cellulose, carboxymethyl cellulose, aluminium stearate gel or hydrogenated edible fats, emulsifying agents, for example lecithin, sorbitan monooleate, or acacia; non-aqueous vehicles (which may include edible oils), for example almond oil, oily esters such as glycerine, propylene glycol, or ethyl alcohol; preservatives, for example methyl or propyl p-hydroxybenzoate or sorbic acid, and, if desired, conventional flavouring or colouring agents.

Suppositories will contain conventional suppository bases, e.g. cocoa-butter or other glyceride.

For parenteral administration, fluid unit dosage forms are prepared utilizing the compound and a sterile vehicle, water being preferred. The compound, depending on the vehicle and concentration used, can be either suspended or dissolved in the vehicle. In preparing solutions the compound can be dissolved in water for injection and filter sterilised before filling into a suitable vial or ampoule and sealing.

Advantageously, agents such as a local anaesthetic, preservative and buffering agents can be dissolved in the vehicle. To enhance the stability, the composition can be frozen after filling into the vial and the water removed under vacuum. The dry lyophilized powder is then sealed in the vial and an accompanying vial of water for injection may be supplied to reconstitute the liquid prior to use. Parenteral suspensions are prepared in substantially the same manner except that the compound is suspended in the vehicle instead of being dissolved and sterilization cannot be accomplished by filtration. The compound can be sterilised by exposure to ethylene oxide before suspending in the sterile vehicle. Advantageously, a surfactant or wetting agent is included in the composition to facilitate uniform distribution of the compound.

The compositions may contain from 0.1% by weight, preferably from 10-60% by weight, of the active material, depending on the method of administration. Where the

compositions comprise dosage units, each unit will preferably contain from 50-500 mg of the active ingredient. The dosage as employed for adult human treatment will preferably range from 100 to 3000 mg per day, for instance 1500 mg per day depending on the route and frequency of administration. Such a dosage corresponds to 1.5 to 50 mg/kg per day. Suitably the dosage is from 5 to 20 mg/kg per day.

No toxicological effects are indicated when a compound of formula (I) or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof is administered in the above-mentioned dosage range.

The compound of formula (I) may be the sole therapeutic agent in the compositions of the invention or a combination with other antibiotics or with a β-lactamase inhibitor may be employed.

Compounds of formula (I) are active against a wide range of organisms including both Gram-negative and Gram-positive organisms.

The following examples illustrate the preparation of certain compounds of formula (I) and the activity of certain compounds of formula (I) against various bacterial organisms.

Novel compounds of formula (I) also form part of the invention. Compounds of the examples are novel.

Example 1. [3R,4R]-3-Ethyl-1-hexyl-4-[3-oxo-3-(6-methoxyquinolin-4-yl)propyl]piperidine.

(a) [3R,4R] 3-Ethyl-4-[3-oxo-3-(6-methoxyquinolin-4-yl)propyl]piperidine.

Hydroquinidine hydrochloride (20g) was dissolved in glacial acetic acid (18ml) and water (150ml) was added. The reaction mixture was refluxed and stirred for 48 hours. The mixture was poured into ice (50g) and sodium hydroxide was added until the solution reached pH12. The mixture was extracted with toluene (3x50ml) then the organic layer was washed with brine, dried over anhydrous magnesium sulphate and evaporated to give an oil. The product was chromatographed on Kieselgel 60 eluting with chloroform/acetone/diethylamine (10:8:1) and gave the title compound (9.56g).
δ_H ($CDCl_3$) 8.82 (d), 8.80 (d), 7.80 (d), 7.50 (d), 7.38 (dd), 3.90 (s), 3.05-2.85 (m), 2.50-2.65 (m), 1.62-1.80 (m), 1.20-1.55 (m), 0.89 (t);
mass spectrum EI, M^+, 326;$C_{20}H_{26}N_2O_2$ requires M, 326.

(b) Title compound

The product from Example 1a (2g) was dissolved in toluene (7ml) and potassium carbonate (1.68g) and 1-bromohexane (1.03ml) were added under nitrogen. The reaction mixture was stirred and refluxed for 7 hours. Water (50ml) was added and the aqueous

phase extracted with toluene (2x75ml). The organic layer was washed with brine, dried over anhydrous magnesium sulphate and evaporated to give an oil. The product was chromatographed on Kieselgel 60 eluting with chloroform/acetone/diethylamine (20:4:1) and gave the title compound (1.9g).

δ_H ($CDCl_3$) 8.84 (d), 8.03 (d), 7.80 (d), 7.60 (d), 7.40 (dd), 3.92 (s), 3.02 (ABq) 2.55 (m), 2.40-2.10 (m), 1.80-1.40 (m), 1.30 (m), 0.90 (2t);
mass spectrum EI M^+, 410. $C_{26}H_{38}N_2O_2$ requires M,410.

Example 2. [3R,4R]-3-Ethyl-1-hexyl-4-[3-(R,S)-hydroxy-3-(6-methoxyquinolin-4-yl)propyl]piperidine.

The product from Example 1b (4.1g) was dissolved in isopropanol (20ml) cooled to -10°C and a suspension of sodium borohydride (443mg) in isopropan-1-ol (45ml) was added in such a way that the temperature did not exceed -5°C. The reaction mixture was stirred for 2hr at -10°C and then water (50ml) was added and the mixture extracted with chloroform (3x100ml). The organic layers were washed with water, brine and then dried over anhydrous magnesium sulphate and finally evaporated to give an oil. The product was chromatographed on Kieselgel 60 eluting with chloroform/diethylamine (20:1) and gave the title compound (3.6g).

δH (d_6DMSO) 8.73 (d), 7.96 (d), 7.57 (d), 7.38 (m), 5.30 (m), 3.91 (s), 2-1.4 (br m), 1.4-1.2 (m), 1-0.7 (m).

The individual diastereomers were separated by preparative HPLC using a Chiralpak AD column.

Example 3. [3R,4R] 3-Ethyl-1-heptyl-4-[3-oxo-3-(6-methoxyquinolin-4-yl)propyl]piperidine.

The product from Example 1a (6.53g) was alkylated using method of Example 1b with 1-bromoheptane (4.3g) to give an oil. The product was chromatographed on Kieselgel 60 eluting with chloroform/acetone/diethylamine (20:4:1) and gave the title compound (6.12g).

δ (CD_3OD) 6.80 (d), 7.97 (d), 7.65 (dd), 7.45 (dd), 4.92 (s), 3.94 (s), 3.31 (m), ca 3.11 (br m), 2.5-2.1 (br m), 1.8-1.4 (br m), 1.3-1.2 (m), 1.0-0.8 (m).

Example 4. [3R,4R]-3-Ethyl-1-heptyl-4-[3-(R,S)-hydroxy-3-(6-methoxyquinolin-4-yl)propyl]piperidine.

The product from Example 3 (6.1g) was reduced by the method of Example 2 to give an oil. The product was chromatographed on Kieselgel 60 eluting with chloroform/diethylamine (20:1) and gave the title compound (5.25g).

δ_H (d_6DMSO) 8.70 (d), 7.95 (d), 7.58 (m), 7.38 (m), 5.30 (m), 3.88 (s), 3.81 (s), 3.40-2.6 (br m), 1.9-1.4 (br m), 1.23 (m), 0.9-0.7 (m).
The individual diastereomers were separated by preparative HPLC using a Chiralpak AD column.

Example 5. [3R,4R] 3-Ethyl-1-octyl-4-[3-oxo-3-(6-methoxyquinolin-4-yl)propyl]piperidine.

The product from Example 1a (2g) was alkylated with 1-bromo octane (1.26ml) using the method of Example 1b to give an oil. The product was chromatographed on Kieselgel 60 eluting with chloroform/diethylamine (20:1) and gave the title compound (2.15g).
δ_H ($CDCl_3$) 8.86 (d) 8.05 (d), 7.83 (d), 7.60 (d), 7.41 (dd), 3.94 (s), 3.02 (ABq), 2.60 (m), 2.36-2.00 (m), 1.80-1.20 (m), 0.91 (t), 0.89 (t);
mass spectrum EI M^+, 438. $C_{28}H_{42}N_2O_2$ requires M, 438.

Example 6. [3R,4R]-3-Ethyl-1-octyl-4-[3-(R,S)-hydroxy-3-(6-methoxyquinolin-4-yl)propyl]piperidine.

The product from Example 5 (1.15g) was reduced by the method of Example 2 to give an oil. The product was chromatographed on Kieselgel 60 eluting with chloroform/diethylamine (20:1) and gave the title compound (0.8g).
δ_H 50/50 mixture of the two isomers ($CDCl_3$) 8.54 (d) 7.92 (d), 7.44 (2d), 7.29 (dd), 7.14, 7.19 (2d), 5.24 (m), 4.6 (m), 3.88 (s), 2.43 (m), 2.3-1.6 (m), 1.6-1.1 (m), 0.90-0.75 (m);
mass spectrum EI M^+, 440. $C_{28}H_{44}N_2O_2$ requires M, 440.

Example 7. [3R,4R]-3-Ethyl-1-decyl-4-[3-oxo-3-(6-methoxyquinolin-4-yl)propyl]piperidine.

The product from Example 1a (2g) was alkylated with 1-bromo decane (1.51ml) using the method of Example 1b to give an oil. The product was chromatographed on Kieselgel 60 eluting with chloroform/diethylamine (20:1) and gave the title compound (1.61g).
δ_H ($CDCl_3$) 8.86 (d), 8.05 (d), 7.82 (d), 7.59 (d), 7.41 (dd), 3.96 (s), 3.05 (ABq), 2.57 (m), 2.36-2.00 (m), 1.80-1.15 (m), 0.93 (t), 0.89 (t);
mass spectrum EI M^+, 466. $C_{30}H_{46}N_2O_2$ requires M, 466.

Example 8. [3R,4R]-3-Ethyl-1-decyl-4-[3-(R,S)-hydroxy-3-(6-methoxyquinolin-4-yl)propyl]piperidine.

The product from Example 7 (1.1g) was reduced using the method of Example 2 give an oil. The product was chromatographed on Kieselgel 60 eluting with chloroform/diethylamine (20.5:5) and gave the title compound (1.13g).
$\delta_H(CDCl_3)$ 50/50 mixture of the two isomers : 8.65 (d), 8.00 (d), 7.50, 7.48 (2d), 7.34 (dd), 7.24, 7.20 (2d), 5.30 (m), 3.91 (s), 3.55 (m), 2.60-1.70 (m), 1.70-1.10 (m) 0.92-0.78 (m);
mass spectrum EI M^+, 468. $C_{30}H_{48}N_2O_2$ requires M, 468.

Example 9. [3R,4R]-3-Ethyl-1-dodecyl-4-[3-oxo-3-(6-methoxyquinolin-4-yl)propyl]piperidine.

The product from Example 1a (2g) was alkylated with 1-bromo dodecane using the method of Example 1b to give an oil. The product was chromatographed on Kieselgel 60 eluting with chloroform/diethylamine (20:1) and gave the title compound (1.42g).
$\delta_H(CDCl_3)$ 8.86 (d), 8.04 (d), 7.82 (d), 7.59 (d), 7.41 (dd), 3.95 (s), 3.02 (ABq), 2.58 (m), 2.35-2.00 (m), 1.80-1.20 (m), 0.91 (t), 0.89 (t);
mass spectrum EI M^+, 494. $C_{32}H_{50}N_2O_2$ requires M, 494.

Example 10. [3R,4R] 3-Ethyl-1-dodecyl-4-[3-(R,S)-hydroxy-3-(6-methoxyquinolin-4-yl)propyl]piperidine.

The product from Example 9 (1.17g) was reduced using the method of Example 2 to give an oil. The product was chromatographed on Kieselgel 60 eluting with chloroform/diethylamine (24:1) and gave the title compound (1.13g).
δ_H $(CDCl_3)$ 50/50 mixture of the two isomers : 8.62 (d), 8.00 (d), 7.50, 7.45 (2d), 7.32 (dd), 7.23, 7.21, (2d), 5.30 (m), 3.91 (s), 3.67 (m), 2.50 (m), 2.35-1.70 (m) 1.70-1.10 (m); 0.95-0.80 (m);
mass spectrum EI M^+, 496. $C_{32}H_{52}N_2O_2$ requires M, 496.

Example 11. [3R,4R]-3-Ethyl-1-cinnamyl-4-[3-(R,S)-hydroxy-3-(6-methoxyquinolin-4-yl)propyl]piperidine.

(a) [3R,4R]-3-Ethyl-4-[3-(R,S)-hydroxy-3-(6-methoxyquinolin-4-yl)propyl]piperidine.

The product from Example 1a (500mg) was reduced using the method of Example 2 to give a pale yellow oil. Column chromatrography on silica gel gave the title compound (315mg) as a white foam.
δ_H $(CDCl_3)$ 8.69 (d, *J*4.5Hz, 1H), 8.0 (d, *J*9.2Hz, 1H), 7.48 (m, 1H), 7.34 (dd, *J* 9.2, 2.7 Hz, 1H), 7.22 (m, 1H), 5.3 (m, 1H), 3.91 (s, 3H); EI M^+, 328 (found: M^+ 328.2149.$C_{20}H_{28}N_2O_2$ requires 328.2151).

(b) Title compound.

The product from Example 11a (205mg) was alkylated with cinnamyl bromide using the method of Example 1b to give a brown oil. Column chromatography on silica gel gave the title compound (73mg) as a pale brown foam.

δ_H ($CDCl_3$) 6.5 (d, *J* 15.8Hz, 1H), 6.26 (dt, *J* 22.5, 7Hz, 1H), 3.09 (ddd, *J* 27.8, 13.5, 6 Hz, 1H); EI, M^+444 (found: M^+ 444.2775.$C_{29}H_{36}N_2O_2$ requires 444.2777).

Example 12. [3R,4R]-3-Ethyl-1-heptyl-4-[3-(6-methoxyquinolin-4-yl)propyl]piperidine.

(a) [3R,4R]-3-Ethyl-4-[3-(6-methoxyquinolin-4-yl)propyl]piperidine.

The product from Example 1a (7.5g) was dissolved in ethylene glycol (20ml) and hydrazine hydrate (1.6ml) was added. The reaction mixture was heated to 145° under a stream of argon for 2 hours. A further 1ml of hydrazine hydrate was added and heating continued for 2 hours. Solid potassium hydroxide (3g) was added over 10 min. and the mixture reheated to 145° for a further 2 hour during which time nitrogen was evolved. The mixture was allowed to cool to room temperature and water (30ml) was added. The mixture was extracted with toluene (4 x 50ml) and the combined extracts dried over anhydrous magnesium sulphate, filtered and evaporated to give a brown oil. Column chromatography on silica gel gave the title compound (5.2g) as an oil.

δ_H ($CDCl_3$) 8.66 (d, *J* 4.4Hz), 8.01 (d, *J* 9.2Hz, 1H), 7.37 (dd, *J* 9.2, 2.8Hz, 1H), 7.22 (dd, *J* 7.8, 2.7 Hz, 1H), 3.95 (s, 3H); EI M^+312 (found: M^+ 312.2207.$C_{20}H_{28}N_2O$ requires 312.2202).

(b) Title compound

The product from Example 12a (312mg) was dissolved in dry dimethylformamide (5ml) and n-heptyl bromide (0.172ml) and potassium carbonate (76mg) were added. The reaction mixture was heated to 80° with stirring for 2 hours, allowed to cool, diluted with water (10ml) and extracted with ethyl acetate (3 x 20ml). The combined organic extracts were dried over anhydrous magnesium sulphate, filtered and evaporated. Column chromatography on silica-gel gave the title compound (283mg) as a white foam.

δ_H($CDCl_3$) 8.68 (d, *J* 4.4Hz, 1H), 8.02 (d, *J* 9.2Hz, 1H), 7.37 (dd, *J* 9.2, 2.8 Hz, 1H), 7.21 (dd, *J* 9.0, 4.5 Hz, 1H), 3.95 (s, 3H), 3.01 (m, 1H); EI M^+410 (found: M^+ 410.3299. $C_{27}H_{42}N_2O$ requires 410.3297).

Example 13. [3R,4R]-3-Ethenyl-1-heptyl-4-[3-(R,S)-hydroxy-3-(6-methoxyquinolin-4-yl)propyl]piperidine

(a) [3R,4R]-3-Ethenyl-4-[3-oxo-3-(6-methoxyquinolin-4-yl)propyl]piperidine.

Quinidine (16.4g) was dissolved in glacial acetic acid (15ml) and water was added (125ml). The reaction mixture was stirred and refluxed for 48 hours. On cooling the pH of the mixture was adjusted to 12 by the addition of sodium hydroxide followed by extraction with toluene (3 x 150ml). The organic layers were combined, dried with anhydrous magnesium sulphate filtered and evaporated to give a brown oil.

(b) [3R,4R]-3-Ethenyl-4-[3-(R,S)-hydroxy-3-(6-methoxyquinolin-4-yl)propyl]piperidine.

The crude product 13a (16g) was reduced by the method of Example 2 to give a pale yellow oil. Column chromatography on silica gel gave the title compound (12.95g) as a white foam.

δ_H ($CDCl_3$) 8.67 (d, *J*4.5Hz, 1H), 8.0 (d, *J* 9.2Hz, 1H), 7.46 (t, *J* 4Hz, 1H), 7.35 (dd, *J* 9.2, 2.7Hz, 1H), 7.22 (dd, *J* 9.3, 2.7Hz, 1H), 6.01 (m, 1H), 5.27 (m, 1H), 5.02 (m, 2H), 3.91 (s, 3H); EI M^+ 326 (found: M^+ 326.1994. $C_{20}H_{26}N_2O_2$ requires 326.1994).

(c) Title compound

The product from Example 13b (12.7g) was alkylated as for Example 3. Column chromatography on silica gel gave the title compound (13.9g) as a white foam.

δ ^1H ($CDCl_3$) 8.69 (d, *J*4.5 Hz, 1H), 8.0 (d, *J* 9.2 Hz, 1H), 7.47 (t, *J* 4.3 Hz, 1H), 7.35 (dd, *J* 9.2, 2.7 Hz, 1H), 7.22 (dd, *J* 9.6, 2.7 Hz, 1H), 6.09 (m, 1H), 5.3 (m, 1H), 5.0 (m, 2H), 3.91 (s, 3H), 0.86 (t, *J* 6.3 Hz, 3H); EI M^+ 424 (found: M^+424.3096.$C_{27}H_{40}N_2O_2$ requires 424.3090).

Example 14. [3R,4R]-3-Ethyl-1-heptyl-4-[3-(R,S)-hydroxy-3-(6-hydroxyquinolin-4-yl)propyl]piperidine

Lithium wire (700mg) was dissolved with stirring in dry tetrahydrofuran (25ml) containing triphenylphosphine (5g) and the mixture stirred at room temperature for 3 hours. The product from Example 4 (426mg) was dissolved in dry tetrahydrofuran (3ml) and 0.694ml of a 1.04M solution of diphenylphosphine in benzene was added followed by 1.87ml of the deep red solution resulting from the reaction of the lithium wiere with triphenylphosphine (as described above).The resulting bright red solution was heated under argon at reflux for 3 hours. A further 0.694ml of a 1.04M solution of diphenylphosphine in benzene and 1.87ml of the solution resulting from the reaction of the lithium wire with triphenylphosphine were added and heating under reflux was continued for 17 hours. The red solution was diluted with chloroform (20ml) and water (10ml) was added. The pH of the reaction mixture was adjusted to 9 with concentrated

hydrochloric acid and the mixture shaken. The aqueous layer was removed and the process repeated with water (1 x 10ml) and brine (1 x 10ml). The organic layer was dried over anhydrous magnesium sulphate, filtered and evaporated to give an orange oil. Column chromatography on silica gel eluting with ethanol/chloroform/0.880 aqueous ammonia solution (15/86/1) gave the title compound (256mg) as a pale cream foam. δ_H ($CDCl_3$) 8.51 (m, 1H), 7.93 (m, 1H), 7.48 (m, 1H), 7.28 (m, 1H), 5.16 (br m, 1H); EI MH^+ 413 (found: MH^+ 413.3166. $C_{26}H_{41}N_2O_2$ requires 413.3168).

Example 15. [3R,4R]-1-Heptyl-3-(2-hydroxyethyl)-4-[3-(R,S)-hydroxy-3-(6-methoxyquinolin-4-yl)propyl]piperidine

The product from Example 13c (424 mg) was treated with 9-borabicyclo[3.3.1]nonane (2.2 ml of a 0.5M solution in tetrahydrofuran) and the reaction mixture was refluxed for 6 hours. The cooled reaction mixture was then treated with ethanol (3 ml), 6 M aqueous sodium hydroxide solution (1 ml) and 30% hydrogen peroxide solution (2 ml). The reaction mixture was stirred at room temperature for 1 hour and extracted with ethyl acetate (3 x 10 ml). The combined organic layers were dried over anhydrous magnesium sulphate and evaporated to give an oil. Column chromatography on silica gel gave the title compound (293 mg) as an oil.
δ_H ($CDCl_3$) 8.71 (m, 1H), 8.02 (d, *J* 9.2Hz, 1H), 7.50 (t, *J* 4.1 Hz, 1H), 7.38 (dd, *J* 9.2, 2.8 Hz, 1H), 7.23 (dd, *J* 4.1, 2.8 Hz, 1H), 5.32 (m, 1H), 3.93 (s, 3H), 3.8 (m, 4H), 3.64 (m, 2H), 2.28 (m, 2H); EI M^+ 442 (found: M^+ 442.3195. $C_{27}H_{42}N_2O_3$ requires 442.3195).
The individual diastereomers were separated by preparative HPLC using a Chiralpak AD column.

Example 16. [3R,4R]-3-Ethyl-1-heptyl-4-[3-(R,S)-hydroxy-3-(6-[5-phthalimidopentyloxy]-quinolin-4-yl)propyl]piperidine.

The product from Example 14 (52mg) was dissolved in dry dimethylformamide (2ml), *N*-5-bromopentylphthalimide (41mg) and potassium carbonate (19mg) were added and the mixture stirred and heated to 80° for 4 hours. The mixture was allowed to cool to room temperature, diluted with water (20ml), the pH adjusted to 12 with potassium carbonate and extracted with ethyl acetate (3 x 50ml). The combined organic layers were dried over anhydrous magnesium sulphate, filtered and evaporated to give a red oil. Colum chromatography on silica-gel eluting with chloroform:ethanol: 0.880 aqueous ammonia solution (84:15:1) gave the title compound (44mg).
δ_H ($CDCl_3$) 8.71 (d, *J* 4.5 Hz, 1H), 7.98 (d, *J* 9.2 Hz, 1H), 7.82 (m, 2H), 7.71 (m, 2H), 7.48 (m, 1H), 7.31 (m, 1H), 7.23 (m, 1H), 5.32 (m, 1H), 4.05 (m, 2H), 3.75 (t, *J* 7.0 Hz, 2H); EI M^+ 627 (found: M^+ 627.4023.$C_{39}H_{53}N_3O_4$ requires 627.4036).

Example 17. [3R,4R]-3-Ethyl-1-heptyl-4-[3-(R,S)-hydroxy-3-(6-[5-aminopentyloxy]-quinolin-4-yl)propyl]piperidine.

The product from Example 16 (4.68g) was dissolved in methanol (20ml) and the solutuion cooled to -40°. Methyl hydrazine (0.794ml) was added and the mixture stirred at -40° for 15 minutes and 2 hours at room temperature. The mixture was evaporated to a red-brown oil, dissolved in methanol (5ml) and fresh methyl hydrozine (800ul) added. After 45 minutes stirring, the reaction mixture was evaporated to low volume and kept under high vacuum for 2 hours to give a red foam. Column chromatography on silica-gel eluting with chloroform:ethanol: 0.880 aqueous ammonia solution (83.5:15:1.5) gave the title compound (3.14g) as a white foam.

δ_H ($CDCl_3$) 8.71 (d, *J* 4.5 Hz, 1H), 8.0 (d, *J* 9.2 Hz, 1H), 7.49 (t, *J* 4.1 Hz, 1H), 7.35 (m, 1H), 7.26 (m, 1H), 5.30 (m, 1H), 4.05 (t, *J* 6.3 Hz, 2H), 2.71 (br t, *J* 6.5 Hz, 2H); CI MH^+ 498.

Example 18. [3R,4R]-3-Ethyl-1-heptyl-4-[3-(R,S)-hydroxy-3-(6-[2-Amino-2-oxo-1,1-dimethyl]ethoxyquinolin-4-yl)propyl]piperidine.

The product from Example 14 (1.39g) was dissolved in dry dioxan (17ml) and sodium hydride (149mg of 60% dispersion in oil) added. The mixture was stirred at room temperature for 1 hour and then 2-bromo-2-methyl-propionamide (560mg) was added and the mixture stirred and heated to 100° for 4 hours. The reaction mixture was allowed to cool to room temperature, the solid sodium bromide filtered off and the dioxan was removed *in vacuo*. The residue was dissolved in chloroform (20ml) and washed with water (2 x 20ml), dried over anhydrous magnesium sulphate, filtered and evaporated to give a brown foam. Column chromatography on silica-gel eluting with chloroform:ethanol:0.880 aqueous ammonia solution (83.5:15:1.5) gave the title compound (853mg) as a white foam.

δ_H ($CDCl_3$) 8.79 (d, *J* 4.5 Hz, 1H), 8.04 (d, *J* 9.15 Hz, 1H), 7.51 (d, *J* 4.5 Hz, 1H), 7.45 (t, *J* 2.7 Hz, 1H), 7.36 (dd, *J* 9.1, 2.6 Hz, 1H), 6.61 (br s, 1H), 5.69 (br s, 1H), 5.26 (br m, 1H), 1.62 (s, 6H); EI M^+497 (found: M^+ 497.3620.$C_{30}H_{47}N_3O_3$ requires 497.3617).

Example 19. [3R,4R]-3-Ethyl-1-heptyl-4-[3-(R,S)-hydroxy-3-(6-[2-hydroxy-2-methyl-propionamido]quinolin-4-yl)propyl]piperidine.

The product from Example 18 (574mg) was dissolved in dry, 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone (0.74ml) in dry dimethylformamide (7.4ml) and sodium hydride (52mg, 60% dispersion in oil) was added. The mixture was stirred and heated to 100° for 3 hours, allowed to cool to room temperature, diluted with water (20 ml) and extracted with chloroform (3x 50 ml). The combined organic layers were dried over anhydrous magnesium sulphate, filtered and evaporated to give a brown oil. Column

chromatography on silica-gel eluting with chloroform : ethanol:0.880 aqueous ammonia (83.5:15:1.5) gave the title compound (257mg).
δ_H ($CDCl_3$) 9.02 (s, 1H), 8.73 (d, *J* 4.5 Hz, 1H), 8.51 (dd, *J* 8.7, 2.1 Hz, 1H), 8.0 (d, *J* 9.0 Hz, 1H), 7.64-7.50 (m, 2H), 5.37 (m, 1H), 2.54 (br s, 1H), 1.61 (s, 6H).

Example 20. [3R,4R]-3-Ethyl-1-heptyl-4-[3-(R,S)-hydroxy-3-(6-aminoquinolin-4-yl)propyl]piperidine

The product from Example 19 (723mg) was dissolved in dioxan (25ml) and 5M hydrochloric acid (25ml) was added. The mixture was stirred and heated to 100° for 2 hours, allowed to cool to room temperature, 10% aqueous sodium carbonate was added to pH12, and extracted with dichloromethane (3 x 50ml). The combined organic layers were dried over anhydrous magnesium sulphate, filtered and evaporated to give a solid. Column chromatography on silica-gel, eluting with chloroform:ethanol: 0.880 aqueous ammonia solution (83.5:15:1.5) gave the title compound (562mg) as a pale brown foam.
δ_H ($CDCl_3$) 8.59 (d, *J* 4.5 Hz, 1H), 7.89 (d, *J* 8.9 Hz, 1H), 7.41 (m, 1H), 7.11 (dd, *J* 8.9, 2.3 Hz, 1H), 7.02 (dd, *J* 8.8, 2.4 Hz, 1H), 5.21 (m, 1H), 4.05 (br s, 2H), 2.56 (br s, 2H); EI M^+ 411 (found: M^+ 411.3233.$C_{26}H_{41}N_3O$ requires 411.3249).

Example 21. [3R,4R]-3-Ethyl-1-heptyl-4-[3-(R,S)-hydroxy-3-(6-azidoquinolin-4-yl)propyl]piperidine.

The product from Example 20 (20mg) was dissolved in 2M hydrochloric acid (1ml) and the solution was cooled to 0° with stirring. Solid sodium nitrite (14mg) was added to the yellow solution which became colouress. The mixture was stirred at 0° for 10 minutes and then sodium azide (40mg) was added. The mixture was allowed to warm to room temperature and stirred for 1 hour. The mixture was diluted with saturated aqueous sodium carbanate solution (5ml) and extracted with dichloromethane (3 x 15ml). The combined organic layers were dried over anhydrous magnesium sulphate, filtered and evaparated to give the title compound (15mg) as a yellow oil.
δ_H ($CDCl_3$) 8.78 (d, *J* 4.5 Hz, 1H), 8.10 (d, *J* 9.0 Hz, 1H), 7.56 (m, 2H), 7.39 (dd, *J* 9.0, 2.4 Hz, 1H), 5.32 (m, 1H), 2.53 (br s, 1H); EI M^+ 437 (found: M^+ 437.3168. $C_{26}H_{39}N_5O$ requires 437.3155).

Example 22. [3R,4R]-3-Ethyl-1-heptyl-4-[3-(6-hydroxyquinolin-4-yl)propyl]piperidine.

(a) [3R,4R]-3-Ethyl-4-[3-(6-hydroxyquinolin-4-yl)propyl]piperidine.

The product from Example 12a (7.0g, 0.022mole) in 47% hydrobromic acid (100ml) was heated at 150°C for 18 hours. The solvent was removed *in vacuo* and the residue basified with saturated sodium hydrogen carbonate solution and evaporated *in*

vacuo. The residue was dissolved in methanol, evaporated *in vacuo* and purified by column chromatography eluting with 20% (9:1 methanol:.880 ammonia)/dichloromethane to afford the title compound (5.5g, 82%) as a grey solid. δ_H ($CDCl_3$) 9.92 (s, 1H), 8.77-8.00 (br s, 1H), 8.53 (d, *J* 6 Hz, 1H), 7.84 (d, *J* 10 Hz, 1H), 7.3-7.19 (m, 3H), 3.43-3.15 (m ,2H), 3.11-2.76 (m, 5H) 1.91-1.50 (m, 5H), 1.49-1.13 (m, 4H), 0.92-0.75 (m, 3H)

(b). Title compound.

The product from Example 22a (3.5g, 0.012 mole) in methanol (100ml) was treated with heptaldehyde (1.6ml, 0,012 mole) and stirred at room temperature for 18 hours. Sodium triacetoxyborohydride (3.72g, 0.018mole) was added and the mixture stirred at room temperature for 4 hours. The solvent was removed in vacuo and the residue partitioned between water and dichloromethane. The dichloromethane layer was dried (magnesium sulphate) and evaporated in vacuo. The residue was purified by column chromatography eluting with 2 to 5% (9:1 methanol/ .880 ammonia)/dichloromethane to afford the title compound (1.7g, 37%) as an orange gum. δ_H ($CDCl_3$) 8.60 (d, *J* 6 Hz, 1H), 8.00 (d, *J* 6 Hz, 1H), 7.50 (br s, 1H), 7.50-7.31 (m ,2H), 7.15 (d, *J* 6 Hz, 1H), 3.00-2.43 (m, 7H), 1.90-0.95 (m, 21H), 0.95-0.74 (m, 6H)
MS (+ve ion electrospray) m/z 397 (MH+).

Example 23. [3R,4R]-3-Ethyl-1-heptyl-4-[3-(6-propyloxyquinolin-4-yl)propyl]piperidine.

The product from Example 22b (0.17g, 0.43mmol) was alkylated with 1-bromopropane(0.044ml, 0.47mmol) by the method of Example 16. Purification by column chromatography eluting with 1 to 2% (9:1 methanol/ .880 ammonia)/dichloromethane afforded the title compound (0.06, 32%) as an orange gum. δ_H ($CDCl_3$) 8.65 (d, *J* 6 Hz, 1H), 8.00(d, *J* 10 Hz, 1H), 7.45-7.10 (m, 3H), 4.05(t, *J* 7 Hz, 2H), 3.14-2.86(m, 2H), 2.70-0.72 (m, 37H)
MS (+ve ion electrospray) m/z 439 (MH+)

Example 24. [3R,4R]-3-Ethyl-1-heptyl-4-[3-(6-(5-Phthalimidopentyloxy)-quinolin-4-yl)propyl]piperidine.

The product from Example 22b (0.15g, 3.8mmol) was alkylated as for Example 16. Purification by column chromatography eluting with 2% (9:1 methanol/ .880 ammonia)/dichloromethane to afforded the title compound (0.11g, 47%) as a colourless oil.

δ_H ($CDCl_3$) 8.67 (d, *J* 5 Hz, 1H), 8.00 (d, *J* 8 Hz, 1H), 7.91-7.80 (m, 2H), 7.78-7.65 (m, 2H), 7.40-7.11 (m, 4H), 4.08 (t, *J* 7 Hz, 2H), 3.75(t, *J* 7 Hz, 2H), 3.10-2.90(m, 2H), 2.68-1.13 (m, 31H), 0.88 (t, *J* 7 Hz, 6H)
MS (+ve ion electrospray) m/z 612 (MH+)

Example 25. [3R,4R]-3-Ethyl-1-heptyl-4-[3-(6-(5-aminopentyloxy)-quinolin-4-yl)propyl]piperidine.

The product from Example 22b (0.10g, 0.16 mmol) in methanol (2ml) was treated with methyl hydrazine as described in Example 17. Purification by column chromatography eluting with 2 to 5% (9:1 methanol/ .880 ammonia)/dichloromethane to afforded the title compound (0.11g, 47%) as a colourless oil.
δ_H ($CDCl_3$) 8.68 (d, *J* 5 Hz, 1H), 8.01 (d, *J* 8 Hz, 1H), 7.42-7.15 (m, 3H), 4.10 (t, *J* 7 Hz, 2H), 3.09-2.86 (m, 2H), 2.83-2.67 (m, 2H), 2.64-1.14 (m, 34H), 0.90 (t, *J* 7 Hz, 6H)
MS (+ve ion electrospray) m/z 482 (MH+)

Example 26. [3R,4R]-3-Ethenyl-1-(2-*t*-butyloxycarbonylaminoethyl)-4-[3-(6-methoxyquinolin-4-yl)propyl]piperidine

(a) [3R,4R]-3-Ethenyl-4-[3-(6-methoxyquinolin-4-yl)propyl]piperidine

Example 13a (50.0g, 154mmol) was reduced as described in Example 12a The product was purified by chromatography on silica gel eluting with 90:9:1 chloroform/ethanol/35% ammonia solution to give the title compound (38.75g, 80%).
δ_H ($CDCl_3$) *inter alia* 8.68 (1H, d, *J* 4.5Hz), 8.02 (1H, d, *J* 9.3Hz), 7.39 (1H, dd, *J* 9.3, 2.7Hz), 7.22 (1H, d, *J* 2.7Hz), 7.19 (1H, d, *J* 4.5Hz), 6.10 (1H, m), 5.06 (2H, m), 3.96 (3H, s). MS (+ve ion electrospray) m/z 311 (MH^+).

(b) [3R,4R]-3-Ethenyl-1-(2-*t*-butyloxycarbonylaminoacetyl)-4-[3-(6-methoxyquinolin-4-yl)propyl]piperidine

N-tert-Butyloxycarbonylglycine (0.14g, 0.008mole) in dry dichloromethane (15ml) was cooled to 0°C and treated with *N*-methylmorpholine (0.096g, 0.00096mole), 1-hydroxybenzotriazole hydrochloride (0.258g, 0.0019mole) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (0.32g, 0.0019mole) and the mixture stirred at 0°C for 30 minutes. The product from Example 26a (0.5g, 0.0016mole) was added and stirred at room temperature for 1 hour. The mixture was washed with saturated aqueous sodium bicarbonate solution, 2M hydrochloric acid and saturated brine solution, dried (magnesium sulphate) and evaporated *in vacuo* . The residue was purified by column chromatography eluting with 5% methanol/dichloromethane to afford the title compound (0.62g, 83%) as a yellow solid.

δ_H ($CDCl_3$) *inter alia* 8.82-8.40 (m, 2H), 7.66-7.20 (m, 4H), 5.89-5.45 (m, 2H), 5.22-5.00 (m, 2H), 4.00 (s, 3H), 1.42 (s, 9H)
MS (+ve ion electrospray) m/z 468 (MH+)

(c) Title compound.

The product from Example 26b (0.61g, 0.0013mole) in dry tetrahydrofuran (10ml) was added dropwise to a suspension of lithium aluminium hydride (0.20g, 0.0052mole) and stirred at room temperature for 16 hours. The mixture was cooled to 0°C and treated dropwise with water (0.2ml), 2m sodium hydroxide solution (0.3ml) and water (0.5ml). The mixture was filtered through celite and the filtrate evaporated *in vacuo*. The residue was purified by column chromatography eluting with 2 to 5% (9:1methanol/.880 ammonia)/dichloromethane to afford the title compound (0.42g, 71%) as an orange oil.

δ_H ($CDCl_3$) 8.66 (d, *J* 7 Hz, 1H), 8.01 (d, *J* 10 Hz, 1H), 7.36 (dd, *J* 3 and 12 Hz, 1H), 7.12 (m, 2H), 6.20-6.01 (m, 1H), 5.10-4.87 (m, 3H), 3.95 (s, 3H), 3.78-3.65 (m, 1H), 3.33-3.11 (m, 3H), 2.97 (t, *J* 7 Hz, 2H), 2.88-2.68 (m, 2H), 2.41-2.25 (m, 3H), 2.18-1.94 (m, 2H), 1.94-2.10 (m, 14H)
MS (+ve ion electrospray) m/z 354 (MH+)

Example 27. [3R,4R]-3-Ethenyl-1-(2-phenoxyethyl)-4-[3-(6-methoxyquinolin-4-yl)propyl]piperidine

(a) [3R,4R]-3-Ethenyl-1-(2-phenoxyacetyl)-4-[3-(6-methoxyquinolin-4-yl)propyl]piperidine.

The product from Example 26a (0.30g, 0.0096mole) in dry dichloromethane (20ml) was treated with triethylamine (0.11g, 0.001mole) and the mixture cooled to 0°C. Phenoxyacetyl chloride (0.18g, 0.001mole) was added and the mixture stirred at room temperature for 2 hours. The mixture was washed with water, dried (magnesium sulphate) and evaporated *in vacuo* to afford the title compound (0.37g, 86%) as a yellow gum.

δ_H ($CDCl_3$) *inter alia* 8.67 (d, *J* 7 Hz, 1H), 8.03 (d, *J* 10 Hz, 1H), 7.40-7.12 (m, 6H), 7.05-6.84 (m, 2H), 5.91-5.48 (m, 1H), 5.19-4.92 (m, 2H), 4.27-4.50 (m, 2H), 3.95 (s, 3H)
MS (+ve ion electrospray) m/z 445 (MH+)

(b) [3R,4R]-3-Ethenyl-1-(2-phenoxyethyl)-4-[3-(6-methoxyquinolin-4-yl)propyl]piperidine

The title compound was prepared from the product from Example 27a using the method of Example 26c.

δ_H ($CDCl_3$) 8.66 (d, *J* 7 Hz, 1H), 8.01 (d, *J* 10 Hz, 1H), 7.41-7.13 (m, 5H), 6.98-6.82 (m, 3H), 6.20-6.01 (m, 1H), 5.08-4.97 (m, 2H), 4.11-4.00 (m, 2H), 3.95 (s, 3H), 3.04-2.62 (m, 6H), 2.40-2.15 (m, 3H), 1.87-1.25 (m, 7H)
MS (+ve ion electrospray) m/z 431 (MH+)

Example 28. [3R,4R]-3-Ethyl-1-(4-ethylbenzyl)-4-[3-(6-methoxyquinolin-4-yl)propyl]piperidine

The title compound was prepared from the product of Example 12a using 4-ethylbenzaldehyde and the method of 22b.
δ_H ($CDCl_3$) 8.68 (d, *J* 6 Hz, 1H), 8.00 (d, *J* 10 Hz, 1H), 7.43-7.03 (m, 7H), 3.95 (s, 3H), 3.41 (q, *J* 7 and 63 Hz, 2H, 3.00 (t, *J* 7 Hz, 2H), 2.78-2.49 (m, 4H), 2.24-1.10 (m, 15H), 0.89-0.71 (m, 3H)
MS (+ve ion electrospray) m/z 431 (MH+)

Example 29. [3S,4R]-3-Ethenyl-1-heptyl-4-[3-(6-methoxyquinolin-4-yl)propyl]piperidine

Example 26a (1.04 g) in water (5 ml) was treated with 5M hydrochloric acid to pH 3.5 followed by a 37% solution of formaldehyde (0.10 g) and the solution was heated under reflux, under argon, for 17 hours. The reaction mixture was evaporated to dryness, dissolved in water and made basic with an excess of 2M sodium hydroxide and extracted with dichloromethane (3 x 20 ml). The organic fraction was washed with water, dried over anhydrous sodium sulphate and evaporated to afford an oil. The oil was dissolved in dry dimethylformamide (5 ml) and anhydrous potassium carbonate (1.84 g) was added, followed by n-heptyl iodide (0.90 g) and the mixture was stirred at room temperature under argon for 17 hours. The reaction mixture was evaporated to dryness, brine was added, and the solution was extracted with dichloromethane (3 x 20 ml). The organic fraction was washed with brine, dried over sodium sulphate, and evaporated to dryness to afford an oil. The crude product was chromatographed on a SepPak 10g silica cartridge eluting with ethyl acetate:hexane (1:1) to afford the title compound as a pale brown oil (0.095 g).
δ_H ($CDCl_3$) 8.65 (d, *J* 4Hz 1H), 8.0 (d, *J* 8Hz, 1H), 7.34 (dd, *J* 8,2 Hz 1H), 7.21 (d, *J* 2Hz, 1H), 7.17 (d, *J* 4Hz), 5.54 (m, 1H), 5.02 (m, 2H), 3.94 (s, 3H), 2.94 (m, 4H), 2.80 (br d, *J* 10 Hz, 2H), 2.27 (m, 2H), 2.02 (m, 2H), 1.10-1.90 (m, 16H), 0.87 (t, *J* 7 Hz, 3H); Found: EI MH^+ 409. $C_{27}H_{40}N_2O$ requires MH, 409.

Example 30 [3R,4R]-3-Ethenyl-1-heptyl-4-[3-(6-methoxyquinolin-4-yl)propyl]piperidine.

Prepared from Example 26a by method of Example 3 in 66% yield.

δ ^1H ($CDCl_3$) 8.57 (d, 1H), 7.95 (d, 1H), 7.09-7.31 (m, 3H), 6.04 (m, 1H), 4.94 (m, 2H), 3.87 (s, 3H), 2.90 (t, 2H), 2.70 (m, 2H), 1.19-2.27 (m, 22H), 0.80 (m, 3H).
EI M^+, 409. $C_{27}H_{40}N_2O$ requires M, 409.

Example 31. [3R,4R]-1-Heptyl-3-(2-hydroxyethyl)-4-[3-(6-methoxyquinolin-4-yl)propyl]piperidine

Prepared from Example 30 (9.95g) using method of Example 15 to give the title compound (1.9g) (22.5%) as an oil.
δ_H ($CDCl_3$) 8.65 (d, 1H), 8.04 (d, 1H), 7.38 (d, 1H), 7.20 (m, 2H), 3.95 (s, 1H).
EI MH^+, 427. $C_{27}H_{42}N_2O_2$ requires MH, 427.

Example 32. [3R,4R]-1-Heptyl-3-(2-acetoxyethyl)-4-[3-(6-methoxyquinolin-4-yl)propyl]piperidine

Example 31 (0.100g) was dissolved in dry pyridine (5 ml) and stirred at room temperature while acetic anhydride (132 ul) and 4-dimethylaminopyridine (catalytic amount) were added. The reaction mixture was stirred at room temperature for 60 hours. The mixture was diluted with ethyl acetate (50 ml), washed with water (3 x 20 ml), dried over anhydrous magnesium sulphate, filtered and evaporated. This gave the title compound (0.083g, 75%) which did not require purification.
δ_H ($CDCl_3$) 1.98 (s, 3H)
EI MH^+, 469. $C_{29}H_{44}N_2O_3$ requires MH, 469.

Example 33. [3R,4R]-1-Heptyl-3-(3-hydroxypropyl)-4-[3-(6-methoxyquinolin-4-yl)propyl]piperidine.

(a) [3R,4R]-1-Benzyloxycarbonyl-3-ethenyl-4-[3-(6-methoxyquinolin-4-yl)propyl]piperidine.

Example (26a) (6.34g) was dissolved in ethyl acetate (70 ml) and saturated aqueous sodium bicarbonate solution (70 ml) was added. Benzyl chloroformate (3.2 ml) was added dropwise to the vigorously stirred reaction mixture while maintaining the pH at 9 by the addition of solid sodium carbonate. Vigorous stirring was continued for 14 hours overnight. Ethyl acetate (20 ml) and water (20 ml) were added and the organic layer separated. The aqueous layer was further re-extracted with ethyl acetate (100 ml), the combined organic layers dried over anhydrous magnesium sulphate, filtered and evaporated. Column chromatography on silica-gel gave the title compound (8.34g, 92%) as an oil.
δ_H ($CDCl_3$) 8.65 (d, 1H), 8.03 (d, 1H), 7.15-7.38 (m, 8H), 5.78 (m, 1H), 5.12 (m, 4H).
EI MH^+, 445. $C_{28}H_{32}N_2O_3$ requires MH, 445.

(b) [3R,4R]-1-Benzyloxycarbonyl-3-(2-hydroxyethyl)-4-[3-(6-methoxyquinolin-4-yl)propyl]piperidine.

The olefin 33a (4.89g, 0.011 moles) was hydroborated as described in Example 15. Column chromatography on silica gel gave a brown coloured oil (3.5g, 69%).

E.I. MH^+, 463. $C_{28}H_{34}N_2O_4$ requires MH, 463.

δ_H ($CDCl_3$) 8.00 (1H, d), 7.25-4 (8H, m), 5.15 (2H, q).

(c) [3R,4R]-1-Benzyloxycarbonyl-3-(2-oxoethyl)-4-[3-(6-methoxyquinolin-4-yl)propyl]piperidine.

The alcohol (33b) (1.5g, 3.24 mmol) was dissolved in dry dichloromethane (40 ml) and size 4A molecular sieves were added. Tetrapropylammonium perruthanate (0.227g, 0.65 mmol) and 4-methyl-mopholine-N-oxide (6.48 mmol) were added to the reaction mixture. This was stirred at room temperature for 1 hour. The reaction mixture was filtered through silica, washing with ethylacetate (50 ml). The organic washings were evaporated. Column chromatography on silica-gel gave a colourless oil (0.56g, 34%).

E.I. MH^+, 461. $C_{28}H_3N_2O_4$ requires MH, 461.

δ_H ($CDCl_3$) 9.65 (1H, m), 8.65 (1H, d), 8.00 (1H, d), 7.1-4 (8H, m), 5.15 (2H, m).

(d) [3R,4R]-1-Benzyloxycarbonyl-3-(prop-2-enyl)-4-[3-(6-methoxyquinolin-4-yl)propyl]piperidine.

Methyltriphenylphosphonium bromide (1.36g, 3.82 mmol) was dissolved in dry tetrahydrofuran (10ml). A solution of potassium tert-butoxide in tetrahydrofuran (1M; 3.3 ml, 3.3 mmol) was added under argon. After 0.25 hours Example 33c (116) (0.5g, 1.09 mmol) in dry THF (10 ml) was added. The reaction mixture was allowed to stir at room temperature for 2 hours. Acetone (10 ml) and ethylacetate (30 ml) were added. The reaction mixture was centrifuged, the supernatent was decanted and the solvent evaporated. Column chromatography on silica-gel gave the olefin as an oil (0.4g, 82%).

E.I. MH^+, 459. $C_{29}H_{34}N_2O_3$ requires MH, 459.

δ_H ($CDCl_3$) 8.65 (1H, d), 8.0 (1H, d), 5.75 (1H, s), 5.15 (2H, s), 5 (1H, m)

(e) [3R,4R]-1-Benzyloxycarbonyl-3-(3-hydroxypropyl)-4-[3-(6-methoxyquinolin-4-yl)propyl]piperidine.

Example 33d (0.31g, 0.676 mmol) was hydroborated as in Example 15. Column chromatography on silica-gel gave the alcohol (0.11g, 34%).

E.I. MH^+, 477. $C_{29}H_{36}N_2O_4$ requires MH, 477.

δ_H ($CDCl_3$) 8.65 (1H, d), 8.0 (1H, d), 7.4-2 (8H, m), 5.15 (2H, m), 3.95 (3H, s).

(f) [3R,4R]-3-(3-Hydroxypropyl)-4-[3-(6-methoxyquinolin-4-yl)propyl]piperidine.

Example 33e (0.11, 0.23 mmol) was hydrogenated under the same conditions as for Example 34b affording the amine as a brown oil (0.071g, 90%).

E.I. MH^+ ,343. $C_{21}H_{30}N_2O_2$ requires MH, 343.

(g) Title compound.

The secondary amine 33f (0.1g, 0.3 mmol) was alkylated as in Example 3. Column chromtography on silica-gel gave the title compound as a clear oil (0.029g, 21%).

E.I. MH^+ ,441. $C_{28}H_{44}N_2O_2$ requires MH, 441.

δ_H ($CDCl_3$) 8.65 (1H, d), 7.95 (1H, d), 7.25 (1H, dd), 7.15 (2H, m), 3.9 (3H, s).

Example 34. [3R,4R]-1-Heptyl-3-(1-hydroxyethyl)-4-[3-(6-methoxyquinolin-4-yl)propyl]piperidine.

(a) [3R,4R]-1-Benzyloxycarbonyl-3-(1-hydroxyethyl)-4-[3-(6-methoxyquinolin-4-yl)propyl]piperidine.

Example 33a (5.72g) was dissolved in THF (30 ml) and mercuric acetate (16.44g) dissolved in THF/water (100 ml/130 ml) added to the solution. The reaction mixture was heated at reflux for 16.5 hours and allowed to cool to room temperature. 2M Sodium hydroxide solution (64 ml) and sodium borohydride (2.00g) dissolved in 2M sodium hydroxide solution (64 ml) were then added to give a grey suspension. After stirring for 3 hours, the mixture was filtered through a plug of celite and washed well with diethyl ether and water. Saturated sodium bicarbonate solution was added and the mixture extracted with diethyl ether and water. Saturated sodium bicarbonate solution was added and the mixture extracted with diethyl ether (x2). The combined organic layers were dried over anhydrous magnesium sulphate, filtered and evaporated. Column chromatography on silica gel gave the title compound (2.32g) (39%) as a white solid.

δ_H ($CDCl_3$) 8.65 (d, 1H), 8.05 (d, 1H), 7.34 (m, 8H), 5.13 (s, 2H), 3.94 (s, 3H), 3.75 (m, 1H), 3.65 (m, 2H), 3.28-2.95 (m, 4H), 2.10 (bs, 1H), 1.20-1.95 (m, H)

EI MH^+ 463. $C_{28}H_{34}N_2O_4$ requires MH, 463.

(b) [3R,4R]-3-(1-Hydroxyethyl)-4-[3-(6-methoxyquinolin-4-yl)propyl]piperidine.

Example 34a (0.700g) was dissolved in ethanol (40 ml), 10% Pd/C (0.400g) added and the reaction mixture hydrogenated at atmospheric pressure for two hours. The mixture was filtered through a small plug of celite and the solvent evaporated to give 0.483g (97%) of the title compound. This was taken onto the next step without purification.

δ_H ($CDCl_3$) 8.65 (D, 1H), 8.03 (d, 1H), 7.38 (d, 1H), 7.23 (m, 2H), 3.94 (s, 1H).

EI MH^+ 329.1. $C_{20}H_{28}N_2O_2$ requires MH, 329.

(c) [3R,4R]-1-Heptyl-3-(1-hydroxyethyl)-4-[3-(6-methoxyquinolin-4-yl)propyl]piperidine.

Example 34b (0.463g) was converted to the title compound by the method of Example 3. Column chromatography on silica gel gave the title compound (0.335g) (56%) as a yellow oil.

δ_H ($CDCl_3$) 8.65 (d, 1H), 8.03 (d, 1H) 7.36 (d, 1H), 7.22 (m, 2H), 3.94 (s, 3H), 3.04-1.27 (m, 3H), 0.88 (m, 3H)

EI MH^+ 427. $C_{27}H_{42}N_2O_2$ requires MH, 427.

Example 35 [3R,4R]-3-Ethyl-1-(2-phenylethyl)-4-[3-(R,S)-hydroxy-3-(6-methoxyquinolin-4-yl)propyl]piperidine.

Example 11a (500 mg, 1.52 mmol) in methanol (30 ml) was stirred with phenyl acetaldehyde (273 mg, 2.28 mmol) and A4 molecular sieves for 30 min, then sodium cyanoborohydride (141 mg, 2.28 mmol) was added and the mixture was stirred overnight. Water (30 ml) was then added and the mixture was extracted with EtOAc (3 x 30 ml). The combined extracts were washed with brine (60 ml), dried (sodium sulphate) and concentrated in *vacuo*. The residual oil was purified by column chromatography (CH2Cl2:MeOH 2-5%) to give the title compound as an oil (610 mg).

δ_H (CDCl3) 8.70 (d, 1H, J=3.3Hz); 8.01 (d, 1H, J=6.6Hz); 7.49 (t, 1H, J=1.65Hz); 7.34 (dd, 1H, J=6.6, 1.65Hz); 7.30-7.15 (m, 6H); 5.31 (m, 1H); 3.90 (s, 3H); 2.81-1.23 (m, 18H); 0.88 (m, 3H)

MS: m/z 433$(MH)^+$

Example 36. [3R,4R]-3-Ethyl-1-(3-phenylpropyl)-4-[3-(R,S)-hydroxy-3-(6-methoxyquinolin-4-yl)propyl]piperidine.

In a manner similar to Example 35 Example 11a (328 mg, 1 mmol) and phenyl propionaldehyde (210 mg, 1.50 mmol) gave the title compound as an oil (388 mg)

δH ($CDCl_3$): 8.72 (d, 1H, J=3.3); 8.01 (d, 1H, J=6.6Hz); 7.48 (t, 1H, J=3.3); 7.34 (dd, 1H, J=6.6,1.65); 7.29-7.14 (m, 6H); 5.32 (m, 1H); 3.92 (s, 3H); 2.70-1.20 (m, 20H); 0.88 (m, 3H)

MS: m/z 447$(MH)^+$

Example 37. 1-Heptyl-4-[2-(R,S)-hydroxy-3-(6-methoxyquinolin-4-yl)propyl]piperidine.

(a) [3R,4R]-1-Benyloxycarbonyl-4-[2-oxo-3-(6-methoxyquinolin-4-yl)propyl]piperidine.

To a solution of lithium diisopropylamide (5.12 ml, 7.68 mmol) in THF (15 ml) at -78°C was added dropwise with stirring a solution of 6-methoxy-4-methylquinoline (1.33 g, 7.68 mmol) in THF (15 ml). The mix. was stirred at -78°c for 20 min. and then a solution of N-(benzyloxycarbonyl)-4-(ethoxyacetyl)-piperidine (1.17 g, 3.84 mmol) in THF (10 ml) was added dropwise. Stirring was continued for 20 min. and allowed to warm to room temp. for 1h. Water added and the aq. layer was neutralised with acetic acid and extracted with EtOAc (X 3). the combined organic layers were washed with brine, dried and concentrated in *vacuo* to give the title compound as an oil. This was purified by column chromatography (Hexane:EtOAc) to give the product as an oil (1.05 g)

MS. : m/z 433 $(M+H)^+$

(b) 1-Benzyloxycarbonyl-4-[2-(R,S)-hydroxy-3-(6-methoxyquinolin-4-yl)propyl]piperidine.

To a solution of Example 37a (114 mg, 0.26 mmol) in MeOH (10 ml) was added excess sodium cyanoborohydride (30 mg) and the reaction mix. was stirred for 2h. Water added and extracted with EtOAc (x3). The combined extracts were washed and concentrated to give the title compound as an oil (112 mg).

MS: m/z 435(MH)+

(c) 4-[2-(R,S)-hydroxy-3-(6-methoxyquinolin-4-yl)propyl]piperidine.

Using the method of Example 34b, Example 37b (550 mg) was hydrogenated to give the title compound as a crystalline product (386 mg) after filtration and concentration in *vacuo*.

MS: m/z 300(MH)+

(d) Title compound.

Example 37c was alkylated as described in Example 22b to give the title compound as an oil (224 mg).

δH: (CDCl3) 8.62 (d, 1H, J=3.3); 8.00 (d, 1H, J=6.6Hz); 7.36 (dd, 1H, J=6.6,1.65); 7.25 (d, 1H, J=1.65); 7.23 (d, 1H, J=3.3); 4.16 (m, 1H); 3.94 (s, 3H); 3.22 (dd, 1H, J=8.26,1.65); 3.05 (dd, 1H, J=8.26,6.6Hz); 2.96 (m, 2H); 2.30 (m, 2H); 1.90-1.189 (m, 19H); 0.87 (t, 3H, J=4.95Hz)

MS: m/z 399$(MH)^+$

Example 38 1-Heptyl-4-[3-(6-methoxyquinolin-4-yl)prop-2-enyl]piperidine.

Example 37 (200 mg, 0.50 mmol) in acetic anhydride (5 ml) was refluxed for 4h. Acetic anhydride was evaporated in *vacuo* and the residue partitioned between saturated

potassium carbonate and EtOAc (20 ml). The organic layer was separated, dried and concentrated in vacuo. Purification by column chromatography (CH_2Cl_2:MeOH:NH_3 ; 9:1:0.1) gave the product as an oil (100 mg)
MS: m/z 381 (MH)

Example 39 1-Heptyl-4-[3-(6-methoxyquinolin-4-yl)propyl]piperidine.

Example 38 (70 mg, 0.18 mmol) in MeOH (50 ml) was reduced with hydrogen in the presence of 10% Pd/C (30 mg) at 50 psi overnight. Concentration of the filtered solution in *vacuo* and purification by column chromatography (CH_2Cl_2:MeOH:NH_3 ; 9:1:0.2) gave the title compound as a crystalline solid (54mg).
(CDCl3) δH: 8.60 (d, 1H, J=3.3Hz); 8.00 (d, 1H, J=6.6Hz); 7.35 (dd, 1H, J=6.6,1.65Hz); 7.22 (d, 1H, J= 1.65Hz); 7.18 (d, 1H, J=3.3Hz); 3.95 (s, 3H); 3.01 (m, 4H); 2.41 (m, 2H); 2.03 (m, 2H); 1.85-1.38 (m,10H); 1.28 (bs, 9H); 0.88 (t, 3H, J=4.95Hz)
MS: m/z 383 $(MH)^+$

Example 40. [3R,4R]-3-Ethyl-1-heptyl-4-[3-(R,S)-hydroxy-3-(6-methoxyquinolin-4-yl)butyl]piperidine

The product from Example 3 (0.49g) was dissolved in dry THF (10ml) and cooled to -78°C under Ar. Methylmagnesium bromide solution (3M in diethyl ether, 0.5ml) was added, and the solution was allowed to warm to ambient temperature over 4h. Water (50ml) was then added, and the mixture was extracted with ethyl acetate (3 x 30ml). The organic layers were washed with brine, dried over anhydrous sodium sulphate and evaporated to give an oil. The product was chromatographed on silica gel, eluting with 0-20% methanol in dichloromethane (gradient), giving first the recovered starting material (0.33g), and then the title compound (0.053g).
δ_H ($CDCl_3$) 8.62 (d), 8.03 (d), 7.99 (d), 7.36 (m), 3.92 (s), 2.9-1.9 (br m), 1.81 (s), 1.6-1.0 (br m), 0.89 (t), 0.78 (t), 0.73 (t);
mass spectrum EI MH^+ 441. $C_{28}H_{44}N_2O_2$ requires MH, 441.

Example 41 [3R,4R]-3-Ethenyl-1-heptyl-4-[3-(R,S)-azido-3-(6-methoxyquinolin-4-yl)propyl]piperidine.

Example 13c (4.8g) was dissolved in dry toluene (15 ml) and diphenylphosphorylazide (2.9 ml) and 1,8-diazabicyclo[5.4.0]undec-7-ene (2.0 ml) were added. The reaction mixture was stirred at room temperature for 21 hours. Further diphenylphosphorylazide (2.9 ml) and 1,8-diazabicyclo[5.4.0]undec-7-ene (2.0 ml) were added and the reaction mixture heated at 50°C for 2 hours 40 minutes. The mixture was allowed to cool to room temperature and saturated sodium bicarbonate solution (50 ml) added. The mixture was extracted with ethyl acetate (3x50 ml) and the combined organic

extracts dried over anhydrous magnesium sulphate, filtered and evaporated. Column chromatography on silica-gel gave the title compound (4.3g, 85%) as a dark yellow oil.
δH ($CDCl_3$) 8.75 (d, 1H), 8.05 (d, 1H), 7.21-7.40 (m, 3H), 6.10 (m, 1H), 5.00 (m, 3H), 3.96 (s, 3H), 2.76 (t, 2H).
EI MH^+ 450. MH of $C_{27}H_{39}N_5O$ requires 450.

Example 42. [3R,4R]-3-Ethenyl-1-heptyl-4-[3-(R,S)-amino-3-(6-methoxyquinolin-4-yl)propyl]piperidine

Example 41 (4.3g) was dissolved in ethanol (100 ml) and 10% Pd/C (1.5g) added. The reaction mixture was hydrogenated at atmospheric pressure for one hour. Approximately 2.3 of the reaction was removed, filtered through a plug of celite and the solvent evaporated. Column chromatography on silica gel gave compound B (1.2g) as a yellow oil.
δH ($CDCl_3$) 8.75 (d, 1H), 8.05 (d, 1H), 7.48 (m, 1H), 7.39 (m, 1H), 7.30 (m, 1H), 6.08 (m, 1H), 4.98 (m, 2H), 4.61 (t, 1H), 3.94 (s, 3H), 2.75 (m, 2H).
EI MH^+ 424. MH of $C_{27}H_{41}N_3O$ requires 424.

Example 43. [3R,4R]-3-Ethyl-1-heptyl-4-(3-(R,S)-amino-3-(6-methoxyquinolin-4-yl)propyl]piperidine

Example 42 was hydrogenated at atmospheric pressure for six hours. The reaction mixture was filtered through a plug of celite and the solvent evaporated. Following a column chromatography on silica gel, title compound was obtained as a yellow oil.
δH ($CDCl_3$) 8.75 (d, 1H), 8.05 (d, 1H), 7.30-7.49 (m, 3H), 4.63 (m, 1H), 3.93 (s, 3H).
EI MH^+ 426. MH of $C_{27}H_{43}N_3O$ requires 426.

Example 44 [3R,4R]-3-Ethyl-1-heptyl-4-[3-(6-methoxyquinolin-4-yl)butyl]piperidine

(a) [3R,4R]-1-Benzyloxycarbonyl-3-ethenyl-4-[3-oxo-3-(6-methoxyquinolin-4-yl)propyl]piperidine.

Example 13a was protected by the method of Example 33a to give the title compound.

(b) [3R,4R]-1-Benzyloxycarbonyl-3-ethenyl-4-[3-(6-methoxyquinolin-4-yl)but-3-en]piperidine.

Example 44a was converted to the title compound by the general method of Example 33d. Chromatography eluting with 5-70% ethyl acetate in petroleum ether afforded the title compound as an oil (2.7g, 72%).

δH ($CDCl_3$) 8.70 (1H, d), 8.05 (1H, d), 7.25-7.40 (7H, m), 7.15 (1H, d), 5.65-5.80 (1H, m), 5.45 (1H, d), 5.00-5.20 (5H, m), 3.90 (3H, s).
E.I. MH^+, 457. $C_{29}H_{32}N_2O_3$ requires MH, 457.

(c) [3R,4R]-3-Ethyl-4-[3-(6-methoxyquinolin-4-yl)butyl]piperidine

Example 44b (0.3g, 0.66 mmol) in tetrahydrofuran (20 ml) was treated with a slurry of 10% palladium on charcoal (0.1g) in water (5 ml) and hydrogenated at atmospheric pressure for 2h. Filtration and evaporated afforded the title compound as a brown oil (0.22g, 100%).
E.I. MH^+, 327. $C_{21}H_{30}N_2O$ requires MH, 327

(d) [3R,4R]-3-Ethyl-1-heptyl-4[3-(6-methoxyquinolin-4-yl)butyl]piperidine

Example 44c was alkylated as described in Example 3. Chromatography, eluting with 1:1 dichloromethane: ethyl acetate afforded the title compound as a clear oil (60 mg, 21%), as a single diastereomer at the benzylic position.
δ ($CDCl_3$) 8.70 (1H, d), 8.05 (1H, d), 7.35 (1H, dd), 7.30 (1H, d), 7.25 (1H, d), 1.35 (3H, d).
E.I. MH^+, 425. $C_{28}H_{44}N_2O$ requires MH, 425

Example 45 [3R,4R]-3-Ethenyl-1-heptyl-4-(3-(R,S)-acetamido-3-(6-methoxyquinolin-4-yl)propyl]piperidine

Acetic anhydride (0.1168g) dissolved in ethyl acetate (1ml) was added dropwise to a vigorously stirred solution of Example 42 (0.440g) in ethylacetate (10ml) and saturated sodium carbonate solution (10ml) at 0°C. The reaction mixture was allowed to warm to room temperature and stirred for 1.5 hours. Additional acetic anhydride (3 drops) in ethyl acetate (1ml) was added dropwise to the reaction mixture and allowed to stir at room temperature overnight. Saturated sodium carbonate solution (20ml) was added and extracted with ethyl acetate (20ml). The organic layer was dried over anhydrous magnesium sulphate, filtered and the solvent evaporated.

Column chromatography on silica gel gave the title compound as an oil (0.390g, 81%)
EI M^+, 466. $C_{29}H_{43}N_3O_2$ requires MH, 466.
δH ($CDCl_3$) 6.10 (m,1H) 5.74 (m, 2H) 5.04 (m, 2H) 2.00 (s, 3H)

Example 46 [3R,4R]-1-Heptyl-3-(2-(R,S)-Hydroxypropyl)-4-[3-(6-methoxyquinolin-4-yl)propyl]piperidine

(a) [3R,4R]-1-Benzyloxycarbonyl-3-(2-(R,S)-Hydroxypropyl)-4-[3-(6-methoxyquinolin-4-yl)propyl]piperidine.

Example 33c was alkylated as described in Example 40 giving the title compound in 13% yield.

E.I. MH^+, 477. $C_{29}H_{36}N_2O_4$ requires MH, 477.

(b) [3R,4R]- 3-(2-(R,S)-Hydroxypropyl)-4-[3-(6-methoxyquinolin-4-yl)propyl]piperidine.

Example 46a was hydrogenated as described for Example 34b to give the title compound in 90% yield.

E.I. MH^+ ,343. $C_{21}H_{30}N_2O_2$ requires MH, 343.

(c) Title compound

Example 46b was alkylated as described for Example 3 to give the title compound in 40% yield.

E.I. MH^+ ,441. $C_{28}H_{44}N_2O_2$ requires MH, 441.

δH ($CDCl_3$) 8.80(d, 1H), 7.95(d, 1H), 7.30(d, 1H), 7.14 (m, 2H), 4.1 (m,1H), 3.9(s,3H).

The individual distereomers were separated using HPLC and a Chiralpak AD column.

Example 47 [3R,4R]-1-Heptyl-3-(1-(R,S),2-dihydroxyethyl)-4-[3-(6-methoxyquinolin-4-yl)propyl]piperidine.

N-methylmorpholine oxide (126 mg) was dissolved in water (5 ml). Acetone (2 ml) and osmium tetroxide (6 mg) in t-butanol (2 ml) added. Example 30 (400 mg) in acetone (3 ml) was added and the reaction mixture stirred at room temperature for 19 hours.

Solid sodium sulfite was added. The mixture was stirred for 30 minutes and then filtered through a plug of celite. The solid was washed well with ethyl acetate and the filtrate dried over anhydrous magnesium sulphate, filtered and evaporated. Column chromatography on silica gel gave the target compound (48 mg) (11%) as a mixture of diastereoisomers (2:1 ratio) as an oil.

δH ($CDCl_3$) 8.55 (d, 1H), 7.95 (d, 1H), 7.30 (d, 1H), 7.14 (m, 2H), 3.88 (m), 3.72 (m), 3.62 (m), 3.50 (m), 3.39 (m), 2.90-3.11 (m, 4H).

EI M^+ 443. $C_{27}H_{42}N_2O_3$ requires MH, 443.

Example 48. [3R,4R]-1-Heptyl-3-aminocarbonyloxyethyl-4-[3-(6-methoxyquinolin-4-yl)propyl]piperidine.

Example 31 (1g, 2.35 mmol) was dissolved in dichloromethane (5 ml). Trichloroacetyl isocyanate (0.5g, 2.5 mmoles) in dichloromethane (1 ml) was added dropwise over 30 minutes. This was stirred at 0°C for 2 hours. Potassium carbonate (0.36g, 2.65 mmoles) in methanol (3 ml) and water (1 ml) was added and the reaction mixture was allowed to stir for an hour at 0°C. The reaction was left to stir at room temperature overnight. The mixture was partitioned between dichloromethane and dilute aqueous sodium bicarbonate and the phases repeated. The organic phase was collected, dried over sodium sulphate and evaporated. Column chromatography on silica gel gave the titlecompound as an oil (0.54g, 49%).

E.I. MH^+, 470. $C_{28}H_{43}N_3O_3$ requires MH, 470.

δH ($CDCl_3$) 8.7 (1H, d), 8.05 (1H, d), 7.35 (1H, dd), 7.25 (2H, m).

Example 49. [3R,4R]-3-Ethyloxycarbonylaminocarbonyloxyethyl-1-heptyl-4-[3-(6-methoxyquinolin-4-yl)propyl]piperidine

Example 31 (0.5g, 1.17 mmol) was dissolved in dichloromethane (5 ml). Ethoxycarbonyl isocyanate (0.124 ml, 1.21 mmol) in dichloromethane (5 ml) was added dropwise over 30 minutes at 0°C. This was left to stir at room temperature overnight. A further portion of ethoxycarbonylisocyanate (0.0612 ml, 0.6 mmol) was added. After two hours saturated sodium bicarbonate solution (50 ml) was added. The mixture was extracted with ethylacetate (3 x 50 ml). The organic extracts were combined and dried over sodium sulphate, filtered and solvent evaporated. Column chromatography on silica-gel gave the product as an oil (0.30g, 5.54 mmol) (47%).

E.I. MH^+,542. $C_{31}H_{47}N_3O_5$ requires MH, 542.

δH ($CDCl_3$) 8.7 (1H, d), 8.05 (1H, d), 7.35 (1H, dd), 7.25 (2H, m), 4.2 (3H, m), 3.95 (3H, s), 3(2H, t).

Example 50. [3R,4R]-3-(1-(R,S)-2-Dihydroxyethyl)-1-heptyl-4-[3-(R,S)-hydroxy-3-(6-methoxyquinolin-4-yl)propyl]piperidine

Prepared as in Example 47 from 0.200g of Example 13c. Column chromatography on silica gel allowed the two pairs of diasteroisomers to be separated by preparative hplc, giving 27mg (25%) of two pairs of diastereomers.

δH ($CDCl_3$) 8.60 (m, 1H), 7.90 (d, 1H), 7.46 (m, 1H), 7.29 (m, 1H), 7.16 (m, 1H), 8.63 (s, 1H), 7.95 (d, 1H), 7.48 (m, 1H), 7.30 (m, 1H), 7.16 (d, 1H).

EI MH^+ 459. $C_{27}H_{42}N_2O_4$ requires MH, 459.

Example 51 [3*R*, 4*R*]-3-Ethyl-1-heptyl-4-[(6-methoxyquinolinyl-4-oxy)methyl]piperidine.

(a) 6-Methoxyquinoline-4-carboxylic acid and [3R,4S]-3-Ethenyl-4-piperidineacetic acid

The title compounds were prepared by modification of the procedure described by W.E. Daering and J.D. Chanley, *J. Amer. Chem. Soc.*, 1946, **68**, 586 whereby quinone (225g, 0.70 mol) in t-butylalcohol (1l) and water (10 ml) was treated with potassium t-butoxide (170g, 1.5 mol). The mixture was stirred at 30C, while air was bubbled through the mixture for 3 days. The mixture was diluted with diethylether and water and the layers separated. The aqueous phase was extracted with ethyl acetate. The combined diethyl ether and ethyl acetate extracts were dried over magnesium sulfate and evaporated to give recovered starting material (97.6g, 43% recovery). The aqueous phase was acidified to pH5 with 5M hydrochloric acid. The precipitate was collected by filtration, washed with water and methanol, then dried to give 6-methoxyquinoline-4-carboxylic acid as a yellow solid (64.6g, 46% yield);
δ_H [$(CD_3)_2SO$, 250 MHz] 6.23-5.95 (1H, m), 5.34-5.06 (2H, m), 3.37-2.92 (5H, m), 2.70 (1H, m), 2.38-2.15 (3H, m), 1.94-1.52 (2H, m): the filtrate contained [3R,4S]-3-Ethenyl-4-piperidineacetic acid.

(b) [3R,4S]-1-(t-Butyloxycarbonyl)-3-ethenyl-4-piperidine acetic acid

[3R,4S]-3-Ethenyl-4-piperidineacetic acid (96g, 0.57 mol) in dichloromethane (900 ml) and methanol (180 ml) was stirred while triethylamine (150 ml, 1.07 mol) were added. The mixture was stirred for 18h and evaporated. The residue was diluted with ethyl acetate and 2.5 m hydrochloric acid. The layers were separated and the aqueous phase extracted twice more with ethyl acetate. The combined organic extracts were extracted three times with sodium carbonate solution. The aqueous extracts were acidified to pH 2.5 with 5M hydrochloric acid and extracted with ethyl acetate three times. The combined organic extracts were washed with brine, dried over magnesium sulfate and evaporated to give the title compound as a buff solid (81.7g, 43%);
δ_H ($CDCl_3$, 250 MHz) 5.89-5.68 (1H, m), 5.23-5.06 (2H, m), 4.12 (1H, brs), 3.95 (2H, d, *J* 13Hz), 3.04 (1H, dd, *J* 3 and 9 Hz), 2.87 (1H, brs), 2.48-2.05 (4H, m), 1.63-1.35 (2H, m), and 1.45 (9H, s).

(c) [3*R*, 4*S*]-1-(*t*-Butyloxycarbonyl)-3-ethyl-4-piperidine acetic acid

Example 51b (2.0g, 7.43mmol) in tetrahydrofuran (100ml) was hydrogenated over 10% palladium on carbon (100mg) for 4 hours. The mixture was filtered through celite and the filtrate concentrated *in vacuo* to give the title compound (2.00g, 100%).
δH ($CDCl_3$) 4.07-3.60 (2H, m), 3.15-2.82 (2H, m), 2.41-2.18 (3H, m), 1.59-1.40 (13H, m), 1.25 (2H, m), 0.98 (3H, t, *J* 7.2Hz). MS (-ve ion electrospray) m/z 270 $[M-H]^-$.

(d) [3*R*, 4*R*]-4-Bromomethyl-1-(*t*-butyloxycarbonyl)-3-ethylpiperidine

Example 51c (1.35g, 5.0mmol) in ethyl acetate (30ml) at 0°C was treated with 4-methylmorpholine (0.6ml, 5.5mmol) and isobutyl chloroformate (0.71ml, 5.5mmol). After 30 minutes at O°C, the resulting suspension was filtered and the filtrate was concentrated. The residue was dissolved in bromotrichloromethane (20ml) and was added dropwise over 5 minutes to a degassed refluxing suspension of 2-mercaptopyridine *N*-oxide sodium salt (894mg, 6.0mmol) in bromotrichloromethane (20ml). After heating under reflux for 1 hour the mixture was cooled and the solution concentrated. The product was purified by chromatography on silica gel eluting with 10% ethyl acetate in hexane to give the title compound as a colourless solid (960mg, 62%).
δH ($CDCl_3$) 4.20-3.82 (2H, m), 3.34 (2H, d, *J* 7.8Hz), 2.92-2.69 (2H, m), 2.02 (1H, m), 1.72 (1H, m), 1.57 (1H, m), 1.52-1.40 (10H, m), 1.20 (2H, m), 0.99 (3H, t, *J* 7.5Hz).

(e) [3*R*, 4*R*]-4-Acetoxymethyl-1-(*t*-butyloxycarbonyl)-3-ethylpiperidine

Example 51d (730mg, 2.38mmol) in acetonitrile (10ml) was added potassium acetate (2.0g, 20.4mmol) and 18-crown-6 (200mg, 0.75mmol). The reaction mixture was heated to reflux for 60 hours and then diluted with chloroform (40ml) and water (5ml). The aqueous phase was re-extracted with chloroform (4 x 40ml) and the combined organic phases dried over magnesium sulphate and concentrated *in vacuo*. The product was purified by chromatography on silica gel eluting with 20% ethyl acetate in hexane to give the title compound (300mg, 44%).
δH ($CDCl_3$) 4.02 (2H, d, *J* 6.9Hz), 4.00-3.70 (2H, m), 3.05-2.78 (2H, m), 2.08 (3H, s), 2.01 (1H, m), 1.61-1.41 (12H, m), 1.22 (2H, m), 0.96 (3H, t, *J* 7.3Hz).
MS (+ve ion electrospray) m/z 287 (MH^+).

(f) [3*R*, 4*R*]-1-(*t*-Butyloxycarbonyl)-3-ethyl-4-(hydroxymethyl)piperidine

Example 51e (110mg, 0.38mmol) was dissolved in methanol (5ml) and treated with 1M aqueous sodium hydroxide (1ml). The reaction mixture was stirred for 18 hours at room temperature and then concentrated *in vacuo*. The residue was partitioned in chloroform and water and the pH of the aqueous phase adjusted to 7 by the addition of dilute aqueous hydrochloric acid. The organic phase was separated and the aqueous phase re-extracted with chloroform. The combined organic phases were dried over magnesium sulphate and concentrated *in vacuo* to yield the title compound (90mg, 97%).
δ ^1H ($CDCl_3$) 4.15-3.83 (2H, m), 3.58 (2H, m), 2.98-2.73 (2H, m), 1.85 (1H, m), 1.65-1.40 (13H, m), 1.25 (2H, m), 0.99 (3H, t, *J* 7.4Hz).

(g) [3*R*, 4*R*]-1-(*t*-Butyloxycarbonyl)-3-ethyl-4-[(6-methoxyquinolinyl-4-oxy)methyl]piperidine

Example 51f (244mg, 1.00mmol) was dissolved in dry DMSO (2ml) and treated with sodium (27mg, 1.17mmol) under argon. The reaction mixture was stirred for 2 hours, treated with 4-chloro-6-methoxyquinoline (244mg, 1.26mmol) and then heated at 60°C for 5 days. The mixture was diluted with water and the product extracted into ethyl acetate (x 3), dried over magnesium sulphate and concentrated *in vacuo*. The product was purified by chromatography on silica gel eluting with ethyl acetate to give the title compound (100mg, 25%).

δH ($CDCl_3$) 8.62 (1H, d, *J* 5.1Hz), 7.95 (1H, d, *J* 9.1Hz), 7.43 (1H, d, *J* 2.7Hz), 7.38 (1H, dd, *J* 9.1, 2.7Hz), 6.72 (1H, d, *J* 5.1Hz), 4.18 (2H, m), 3.94 (3H, s), 3.03 (2H, m), 2.42 (1H, m), 1.87 (1H, m), 1.75-1.43 (13H, m), 1.37 (2H, m), 1.02 (3H, t, *J* 7.3Hz). MS (+ve ion electrospray) m/z 401 (MH^+).

(h) [3R,4R]-3-Ethyl-4-[(6-methoxyquinolinyl-4-oxy)methyl]piperidine *bis*-trifluoroacetate.

Example 51g (100mg, 0.25mmol) was dissolved in dichloromethane (2ml), cooled to 0°C and treated with trifluoroacetic acid (2ml). The reaction mixture was allowed to warm to room temperature and stirred for a further 3 hours. The mixture was concentrated *in vacuo*, re-suspended in toluene and concentrated (x 3) to yield the title compound (130mg, 100%).

δH (d_6DMSO) 9.09 (1H, d, *J* 6.5Hz), 8.52 (2H, br s, exch), 8.11 (1H, d, *J* 9.3Hz), 7.78 (1H, dd, *J* 9.3, 2.7Hz), 7.58 (1H, d, *J* 6.6Hz), 7.53 (1H, d, *J* 2.7Hz), 5.02 (1H, br s, exch), 4.56 (2H, m), 3.96 (3H, s), 3.18-3.03 (4H, m), 2.62-1.83 (4H, m), 1.44 (2H, m), 0.97 (3H, t, *J* 7.3Hz). MS (+ve ion electrospray) m/z 301 (MH^+).

(i) Title compound.

Example 51h (120mg, 0.23mmol) in DMF (3ml) was treated with potassium carbonate (125mg, 0.91mmol) and 1-iodoheptane (41ul, 0.25mmol). The mixture was stirred at room temperature for 3 hours and then concentrated *in vacuo*. The residue was redissolved in ethyl acetate, washed with water (x 2), dried over magnesium sulphate and concentrated *in vacuo*. The product was purified by chromatography on silica gel eluting with 95:4.5:0.5 chloroform/ ethanol/ 35% ammonia solution to give the title compound (80mg, 87%).

δH ($CDCl_3$) 8.62 (1H, d, *J* 5.2Hz), 7.94 (1H, d, *J* 9.2Hz), 7.47 (1H, d, *J* 2.7Hz), 7.35 (1H, dd, *J* 9.2, 2.7Hz), 6.72 (1H, d, *J* 5.2Hz), 4.16 (2H, m), 3.94 (3H, s), 2.62 (2H, m), 2.41-2.20 (5H, m), 1.95-1.25 (15H, m), 0.98 (3H, t, *J* 7.4Hz), 0.88 (3H, t, *J* 6.8Hz). MS (+ve ion electrospray) m/z 399 (MH^+).

Example 52 [3R,4S]-3-Ethenyl-1-heptyl-4-[2-(6-methoxyquinolin-4-yl)-oxyethyl]piperidine.

(a) Methyl [3R,4S]-3-ethenyl-4-piperidine acetate hydrochloride

Thionyl chloride (20ml) was added dropwise to a solution of Example 51b (10.0g, 37.1mmol) in methanol (400ml). The mixture was heated at reflux for 4 hours and then concentrated *in vacuo*. The residue was diluted with toluene and concentrated (x 3) to yield the title compound (8.10g, 100%).

δH (d_6 DMSO) 9.18 (1H, br s, exch.), 8.82 (1H, br s, exch), 6.03 (1H, m), 5.14 (2H, m), 3.59 (3H, s), 3.20-2.91 (4H, m), 2.62 (1H, m), 2.33-2.20 (3H, m), 1.80-1.52 (3H, m). MS (+ve ion electrospray) m/z 184 (MH^+).

(b) Methyl [3R,4S]-1-heptyl-3-ethenyl-4-piperidine acetate

Example 52a (8.1g, 36.9mmol) was alkylated as described in Example 12b The product was purified by chromatography on silica gel eluting with 50% ethyl acetate in hexane to give the title compound (9.71g, 94%).

δH ($CDCl_3$) 6.08 (1H, m), 5.03 (2H, m), 3.68 (3H, s), 2.79-2.62 (2H, m), 2.42-1.20 (20H, m), 0.89 (3H, t, *J* 6.7Hz). MS (+ve ion electrospray) m/z 282 (MH^+).

(c) [3R,4S]-1-Heptyl-3-ethenyl-4-(2-hydroxyethyl)-piperidine.

Lithium aluminium hydride (750mg, 19.7mmol) was added to a solution of Example 52b (2.5g, 9.8mmol) in tetrahydrofuran (100ml) at 0°C and the mixture stirred for 1 hour at that temperature. Water (0.75ml) was added, followed by 10% aqueous sodium hydroxide solution (1.1ml) and then water (1.9ml). The mixture was stirred for 1 hour and then filtered. The filtrate was concentrated *in vacuo* to yield the title compound as a orange oil (2.5g, 100%).

δH ($CDCl_3$) 6.12 (1H, m), 5.05 (2H, m), 3.67 (2H, t, *J* 6.5Hz), 2.76 (2H, m), 2.38-1.20 (21H, m), 0.89 (3H, t, *J* 6.8Hz). MS (+ve ion electrospray) m/z 254 (MH^+).

(d) [3R,4S]-3-Ethenyl-1-heptyl-4-[2-(6-methoxyquinolin-4-yl)oxyethyl]piperidine.

Diethyl azodicarboxylate (140ul, 0.88mmol) was added to a solution of 4-hydroxy-6-methoxyquinoline (100mg, 0.58mmol), Example 52c (160mg, 0.64mmol) and triphenylphosphine (224mg, 0.86mmol) in tetrahydofuran (10ml). The reaction mixture was stirred at room temperature for 18 hours and then diluted with diethyl ether and dilute aqueous hydrochloric acid. The aqueous phase was separated, washed with diethyl ether (x 2) and then basified with aqueous potassium carbonate solution. The product was extracted with dichloromethane (x 2), dried over magnesium sulphate and concentrated *in vacuo*. The product was purified by chromatography on silica gel eluting

with 97:2.7:0.3 chloroform/ ethanol/ 35% ammonia solution to give the title compound (65mg, 55%).

δH ($CDCl_3$) 8.61 (1H, d, *J* 5.3Hz), 7.95 (1H, d, *J* 9.2Hz), 7.46 (1H, d, *J* 2.8Hz), 7.36 (1H, dd, *J* 9.2, 2.8Hz), 6.70 (1H, d, *J* 5.3Hz), 6.19 (1H, m), 5.14 (2H, m), 4.23 (2H, m), 3.96 (3H, s), 2.80 (2H, m), 2.47-2.05 (5H, m), 1.88 (3H, m), 1.69 (2H, m), 1.46 (2H, m), 1.34-1.21 (8H, m), 0.88 (3H, t, *J* 6.8Hz). MS (+ve ion electrospray) m/z 411 (MH^+).

Example 53 1-Heptyl-4-[(6-methoxyquinolin-4-yl)oxymethyl]piperidine

(a) Ethyl 1-heptylpiperidine-4-carboxylate

Ethyl isonipecotate (5.0g, 31.8mmol) was dissolved in 1,2-dichloroethane (100ml) and treated with 1-heptaldehyde (4.4ml, 31.5mmol). The reaction mixture was stirred for 10 minutes and then sodium triacetoxyborohydride (6.7g, 31.7mmol) was added. After stirring for 18 hours, the reaction was diluted with dichloromethane and aqueous sodium carbonate solution. The organic phase was dried over magnesium sulphate, filtered and concentrated *in vacuo*. The product was purified by chromatography on silica gel eluting with ethyl acetate to give the title compound (2.60g, 32%).

δH ($CDCl_3$) 4.14 (2H, q, *J* 7.1Hz), 2.90 (2H, m), 2.32-2.23 (3H, m), 2.04-1.69 (7H, m), 1.49 (2H, m), 1.33-1.21 (10H, m), 0.89 (3H, t, *J* 6.9Hz). MS (+ve ion electrospray) m/z 256 (MH^+).

(b) 1-Heptyl-4-hydroxymethylpiperidine

Lithium aluminium hydride (1.0g, 26.3mmol) was added to a solution of ethyl 1-heptylpiperidine-4-carboxylate (2.2g, 8.6mmol) in tetrahydrofuran (100ml) at 0°C. The reaction mixture was allowed to warm to room temperature and stirred for a further 66 hours. Water (1ml) was added, followed by 10% aqueous sodium hydroxide solution (1.5ml) and then water (2.5ml). The mixture was stirred for 1 hour and then filtered. The filtrate was concentrated *in vacuo* to yield the title compound as a yellow oil (1.84g, 100%).

δH ($CDCl_3$) 3.48 (2H, d, *J* 6.4Hz), 2.96 (2H, m), 2.30 (2H, m), 1.95-1.20 (18H, m), 0.89 (3H, t, *J* 6.8Hz). MS (+ve ion electrospray) m/z 213 (MH^+).

(c) 1-Heptyl-4-[(6-methoxyquinolin-4-yl)oxymethyl]piperidine

1-Heptyl-4-hydroxymethylpiperidine was treated with 4-chloro-6-methoxyquinoline (90mg, 0.47mmol) using the general method of Example 51g to give the title compound (84mg, 48%).

δH ($CDCl_3$) 8.61 (1H, d, *J* 5.2Hz), 7.96 (1H, d, *J* 9.1Hz), 7.47 (1H, d, *J* 2.8Hz), 7.35 (1H, dd, *J* 9.1, 2.8Hz), 6.70 (1H, d, *J* 5.2Hz), 4.05 (2H, d, *J* 6.4Hz), 3.95 (3H, s), 3.03

(2H, m), 2.37 (2H, m), 2.09-1.22 (17H, m), 0.85 (3H, t, *J* 6.7Hz). MS (+ve ion electrospray) m/z 371 (MH^+).

Example 54 [3R,4R]-3-Ethyl-1-heptyl-4-[(6-methoxyquinolin-4-yl)methylthiomethyl]piperidine

(a) [3R,4R]-1-(*t*-Butyloxycarbonyl)-3-ethylpiperidine-4-methylthioacetate

Example 51f (612mg, 2mmol) and potassium thioacetate (342mg, 3mmol) in acetone (20ml) was heated under reflux under argon for 2 hours. After cooling to room temperature the solution was concentrated and the residue purified by rapid chromatography on silica gel eluting with 10% ethyl acetate in hexanes to give the title compound as a gum (500mg, 83%).

δH ($CDCl_3$) 4.20-3.80 (2H, m), 3.00-2.70 [4H, m including δ 2.85 (2H, d, *J* 7.5Hz], 2.34 (3H, s), 1.80-1.10 [17H, m including δ 1.45 (9H, s)], 0.97 (3H, t, *J* 7.5Hz).

(b) 4-Chloromethyl-6-methoxyquinoline

4-Hydroxymethyl-6-methoxyquinoline {A. Knoll, Patent DE 88044, 1950} (2.0g, 10.6mmol) was suspended in dichloromethane (100ml) and treated with thionyl chloride (3ml, 41.1mmol). The reaction mixture was stirred at room temperature for 18 hours and then concentrated *in vacuo*. The residue was re-suspended in toluene and concentrated (x3). The resulting solid was partitioned between dichloromethane and saturated sodium hydrogen carbonate solution, the organic layer was separated washed with brine, dried over magensium sulphate to give the title compound as a colourless solid.

δH ($CDCl_3$) 8.75 (1H, d, J 5.0Hz), 8.06 (1H, d, J 9.2Hz), 7.44-7.38 (2H, m), 7.30 (1H, d, J 2.8Hz), 4.96 (2H, s), 3.98 (3H, s). MS (+ve ion electrospray) m/z 208, 210 (MH^+).

(c) [3R,4R]-3-Ethyl-4-[(6-methoxyquinolin-4-yl)methylthiomethyl]piperidine

A solution of [3R,4R]-1-(*t*-butyloxycarbonyl)-3-ethylpiperidine-4-methylthioacetate (400mg, 1.33mmol) in *N,N*-dimethylformamide (5ml) and sodium methoxide (143mg, 2.66mmol) was stirred at room temperature under argon for 20 minutes. A solution of 4-chloromethyl-6-methoxyquinoline (269mg, 1.33mmol) was then added and the mixture was heated at 80°C for 2 hours. After cooling to room temperature the mixture was diluted with water and ethyl acetate. The organic layer was separated, washed with brine, dried over magnesium sulphate and concentrated. The residue was purified by chromatography on silica gel eluting with 50-100% ethyl acetate in hexanes to give [3R,4R]-1-(t-butyloxycarbonyl)-3-ethyl-4-[(6-methoxyquinolin-4-yl)methylthiomethyl]piperidine (154mg, 48%).

This material was deprotected by the general method of Example 51h to give the title compound (39mg, 34%) as a gum.

δH (CDCl3) 8.69 (1H, d, *J* 4.3Hz), 8.03 (1H, d, *J* 9.1Hz), 7.41-7.25 (3H, m), 4.07 (3H, s), 3.96 (2H, s), 3.00-2.30 (6H, m), 1.95-1.05 (7H, m), 0.85 (3H, t, *J* 7.1Hz). MS (+ve ion electrospray) m/z 331 (MH^+).

(d) Title compound

Example 54c (33mg, 0.1mmol) was alkylated by the method of Example 22b to give the title compound (28mg, 65%) as a gum.
δH ($CDCl_3$) 8.69 (1H, d, *J* 4.3Hz), 8.03 (1H, d, *J* 9.1Hz), 7.40-7.26 (3H, m), 4.06 (2H, s), 3.96 (3H, s), 2.60-1.05 (24H, m), 0.85 (6H, m). MS (+ve ion electrospray) m/z 429 (MH^+).

Example 55 [3R,4R]-1-Heptyl-3-ethenyl-4-[{(6-methoxyquinoline-4-yl)carbonylamino}methyl]piperidine

(a) [3R,4R]-1-*tert*-Butoxycarbonyl-3-ethenyl 4-{[(2-trimethylsilylethoxy)carbonylamino]methyl}-piperidine.

To a solution of Example 51c,(5.4g, 20 mmol) 2-trimethylsilylethanol (4.7 ml, 22 mmol) and triethylamine (3.1 ml, 22 mmol) in xylene was added diphenylphosphoryl azide (3.1 ml, 22 mmol) and the mixture was heated under reflux for 7 h. After cooling, the mixture was washed with saturated aqueous sodium bicarbonate and brine, dried and evaporated. The crude product was chromatographed on silica gel (400g) eluted with 4:1 hexane/ethyl acetate to give the title compound, 3.04g (40%).
m.s. 407 ($M.Na^+$), 351, 307.

(b) [3R,4R]-Aminomethyl-1-*tert*-butoxycarbonyl-3-ethenylpiperidine.

To a solution of tetrabutylammonium fluoride (1M in tetrahydrofuran, 33 ml) was added Example 55a (3.03g, 7.9 mmol), and the mixture was stirred at 30°C for 64 h. Solvent was removed *in vacuo* and the residue was dissolved in dichloromethane and washed with saturated aqueous ammonium chloride. The organic phase was dried and evaporated, and the residue was chromatographed on silica gel (400g) eluted with 5-20% methanol/dichloromethane, with addition of 1% triethylamine in the later stages. Eluted product was dissolved in water and extracted with dichloromethane. The organic extract was washed with water, dried and evaporated to give the title compound, 0.39g (21%).
m.s. 241 (MH^+), 185, 141

(c) [3R,4R]- 1-*tert*-Butoxycarbonyl-3-ethenyl-4-[{(6-methoxyquinoline-4-yl)carbonylamino}methyl]piperidine.

A mixture of Example 55b (0.39g, 1.6 mmol), 6-methoxy-4-quinoline carboxylic acid (0.32g, 1.6 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride

(0.30g, 1.6 mmol) and 1-hydroxybenzotriazole monohydrate (50 mg) in dimethylformamide (10 ml) was stirred for 6h at room temperature. Solvent was removed *in vacuo* and the residue was partitioned between ethyl acetate and sat. aqueous sodium bicarbonate. The organic phase was washed with water, dried and evaporated. The residue was chromatographed on silica gel (40g) eluted with ethyl acetate to give the title compound, (0.56g) (82%).
m.s. 426 (MH^+), 370, 326

(d) [3R,4R]-3-Ethenyl-4-[{(6-methoxyquinoline-4-yl)carbonylamino}methyl]piperidine

Example 55c was deprotected with trifluoroacetic acid by the method of Example 51h to give the title compound, 0.77g (100%).
m.s. 326 (MH^+)

(e) Title compound

Example 55d (0.60g) was alkylated by the method of Example 3 to give the title compound, 0.30g (64%).
^1H NMR ($CDCl_3$) δ: 0.88 (3H, m), 1.27 (8H, m), 1.44 (2H, m), 1.65 (2H, m), 1.93 (1H, m), 2.05 (1H, m), 2.16-2.33 (2H, m), 2.46 (1H, m), 2.78-2.87 (2H, m), 3.38 (1H, quintet, J=7), 3.49 (1H, quintet, J=7), 3.92 (3H, s), 5.12 (2H, d, J=13), 6.16 (1H, s), 6.25 (1H, dd, J=18, 9), 7.34 (1H, d, J=4), 7.40 (1H, dd, J=9,2), 7.54 (1H, d, J=2), 8.01 (1H, d, J=9), 8.76 (1H, d, J=4).
m.s. 424 (MH^+)

Example 56 [3R,4R]-3-Ethenyl-1-heptyl-piperidine-4-[N-(6-methoxyquinolin-4-yl)]propionamide.

(a) [3R,4R]-Methyl 3-[1-t-butyloxycarbonyl-3-ethenyl-piperidin-4-yl]propanoate

Example 51b (1.5g, 5.58 mmol) in ethyl acetate at 0°C was treated with N-methylmorpholine (0.72 ml, 6.56 mmol), then isobutylchloroformate (0.90 ml, 6.94 mmol). The mixture was stirred for 0.75h, then filtered and kept cold while a solution of diazomethane in ether (generated from diazolol (10.75g, 50 mmol)] was added. The mixture was stirred for 18h, then the solvent removed by blowing a stream of argon through the mixture. The crude product was purified on silica gel 60 eluting with 1:2 ethylacetate, hexane to give [3(R),4(S)-1-(t-butyloxycarbonyl)-3-ethenyl-4-piperidinylmethyl]diazomethylketone as a yellow oil (0.83g, 50%); ν_{max} (CH_2Cl_2) 2101, 1734, 1692, 1642 cm^{-1}. The diazoketone (0.83g, 2.83 mmol) in methanol (30 ml) was treated with silver benzoate (2.05 mmol) and triethylamine (4.7 ml, 33.6 mmol). The mixture was stirred for 3 days with the exclusion of light. The mixture was

evaporated and the amide product purified by chromatography on silica gel eluting with 3.7 ethylacetate, hexane to give the title compound as a yellow oil (0.61g, 73% yield); δ_H ($CDCl_3$, 250 MHz) 5.91-5.70 (1H, m), 5.18-5.04 (2H, m), 4.11 (1H, brs), 3.98 (1H, d, *J* 13Hz), 3.67 (3H, s), 2.96 (1H, dd, *J*3 and 16Hz), 2.77 (1H, br s), 2.32 (2H, m), 1.56 (2H, m) and 1.44 (9H, s).

(b) [3R,4R]-3-[1-t-Butyloxycarbonyl-3-ethenyl-piperidin-4-yl]propanoic acid.

Example 56a (0.15g, 0.505 mmol) in dioxan (5 ml) with 40% aqueous sodium hydroxide solution (0.1 ml) was stirred at room temperature for 18h, then heated at 80°C for 6h. The mixture was diluted with ethyl acetate and acidified with 5N hydrochloric acid. The layers were separated and the aqueous phase extracted twice more with ethyl acetate. The combined organic extracts were washed with brine, dried over magnesium sulfate and evaporated to give the title compound as a pale yellow oil (0.14g, 98% yield); δ_H ($CDCl_3$, 250 MHz) 5.90-5.67 (1H, m), 5.16-5.04 (2H, m), 4.12 (1H, m), 3.99 (1H, d, *J* 11 Hz), 2.95 (1H, dd, *J*3 and 13Hz), 2.77 (1H, brs), 2.36 (3H, m), and 1.57 (2H, m); m/z (negative electrospray) $[M-H]^+$292.

(c) [3R,4R]-3-Ethenyl-1-(t-butyloxycarbonyl)-piperidine-4-[N-(6-methoxyquinolin-4-yl)]propionamide

Example 56b (0.14g, 0.50 mmol) in dichloromethane (20 ml) was treated with oxalyl chloride (0.07 ml, 0.80 mmol) and N,N-dimethylformamide (1 drop). The mixture was stirred for 1h, then evaporated to dryness. The residue was diluted with toluene and dichloromethane and evaporated.

The acid chloride was dissolved in dichloromethane (10 ml) and added to a mixture of 4-amino-6-methoxyquinoline (0.09g, 0.44 mmol) and triethylamine (0.14 ml, 1.0 mmol) in dichloromethane (10 ml). The mixture was stirred for 2h, then diluted with dichloromethane and washed successively with water and brine. The solution was dried over magnesium sulfate and evaporated to give the title compound as an oil (0.087g, 40% yield);

δ_H ($CDCl_3$, 250 MHz) 8.71 (1H, d, *J* 5Hz), 8.16 (1H, s), 8.03 (1H, d, *J* 9Hz), 7.82 (1H, s), 7.39 (1H, dd, *J* 2.54 and 9Hz), 7.02 (1H, d, *J* 2.5 Hz), 5.93-5.74 (1H, m), 5.25-5.08 (2H, m), 4.25-3.90 (2H, m), 3.94 (3H, s), 2.96 (1H, d, *J* 14.5 Hz), 2.79 (1H, brs), 2.55 (1H, m), 2.36 (1H, m), 1.73 (4H, s) and 1.45 (9H, s).

(d) Title compound

Example 56cwas deprotected with trifluoroacetic acid (2ml) as described in Example 51h. The crude amine was alkylated as described in Example 12b. The crude

product was purified on silica gel eluting with 1-4% methanol in dichloromethane to give a colourless glass (0.047g, 58% yield);
δ_H ($CDCl_3$, 250 MHz)8.69 (1H, m), 8.19-8.04 (1H, m), 8.00 (1H, d, *J* 10 Hz), 7.30 (1H, dd, *J* 2.5 and 9.5 Hz), 7.06 (1H, d, *J* 3 Hz), 6.21-6.02 (1H, m), 5.13-5.01 (2H, m), 3.90 (3H, s), 2.89-2.68 (2H, m), 2.53-2.42 (2H, m), 2.42-2.09 (6H, m), 2.09-1.94 (1H, m), 1.72-1.60 (2H, m), 1.59-1.37 (4H, m), 1.27 (7H, s) and 0.88 (3H, m); m/z (positive electrospray) MH^+ 438.

Example 57 [3R,4R]-3-Ethenyl-1-heptyl-piperidine-4-[N-(6-methoxyquinolin-4-yl)]propylamine.

Example 56d (0.019g, 0.045 mmol) in tetrahydrofuran (4 ml) was treated with 1M lithium aluminium hydride (0.15 ml) and heated at reflux for 2h. The mixture was then allowed to cool and diluted with water (0.2 ml) and 40% aqueous sodium hydroxide (0.1 ml). The mixture was evaporated and the crude product purified on silica gel eluting with 5% methanol in chloroform containing 0.5% 0.88 ammonia to give the title compound as an oil (0.014g, 76% yield);
δ_H ($CDCl_3$, 250 MHz) 8.45 (1H, d, *J* 5Hz), 7.91 (1H, d, *J* 9Hz), 7.40-7.22 (1H, m), 6.95 (1H, s), 6.40 (1H, d, *J* 5Hz), 6.37-6.04 (1H, m), 5.22-4.96 (2H, m), 4.80 (1H, s), 3.92 (3H, s), 3.28 (2H, m), 2.80 (2H, m), 2.45-1.90 (4H, m), 1.90-1.10 (9H, m), 0.88 (3H, m); m/z (positive electrospray) MH^+ 424.

Example 58 [3R,4S]-3-Ethenyl-1-heptyl-piperidine-4-[N-(6-methoxyquinolin-4-yl)]acetamide.

The title compound was prepared by the methods of Examples 56c and 56d from Example 51b and 4-amino-6-methoxyquinoline.

The crude product was chromatographed on silica gel, eluting with 0-5% methanol in dichloromethane (gradient), giving the title compound as a colourless glass.
δ_H ($CDCl_3$) 8.68 (d), 8.39 (s), 8.16 (d), 7.97 (d), 7.33 (dd), 7.08 (d), 6.17 (m), 5.15-5.0 (m), 3.83 (s), 2.9-2.6 (m), 2.5-1.95 (m), 1.75-1.2 (m), 0.88 (t);
mass spectrum EI MH^+ 424 ($C_{26}H_{37}N_3O_2$).

Example 59 [3R,4R]-3-Ethenyl-1-heptyl-piperidine-4-[N-(6-methoxyquinolin-4-yl)]ethylamine.

The product from Example 58 (0.33g) was reduced by the method of Example 57. Chromatographed on silica gel, eluting with 0-12% (9:1 ethanol / 880 ammonia) in dichloromethane (gradient), gave the title compound (0.24g) as a yellow gum which solidified slowly on standing.

δ_H ($CDCl_3$) 8.42 (d), 7.90 (d), 7.28 (dd), 7.00 (d), 6.40 (d), 6.15 (m), 5.2-5.0 (m), 3.88 (s), 3.72 (m), 3.4 (b), 3.30 (m), 2.77 (m), 2.4-2.0 (m), 1.75-1.2 (m), 0.88 (t); mass spectrum EI MH^+ 410 ($C_{26}H_{39}N_3O$).

Example 60 [3R,4S]-3-Ethenyl-1-heptyl-4-[2-(R,S)-hydroxy-2-(6-methoxyquinolin-4-yl)ethyl]piperidine

(a) [3R,4R]-1-(t-Butoxycarbonyl)-3-ethenyl-4-[1-(R,S)-methoxycarbonyl-2-oxo-2-(6-methoxyquinolin-4-yl)ethyl]piperidine and [3R,4R]-1-(methoxycarbonyl)-3-ethenyl-4-[1-(R,S)-methoxycarbonyl-2-oxo-2-(6-methoxyquinolin-4-yl)ethyl]piperidine

Sodium amide (90%; 2.0 g) was added cautiously to a mixture of methyl [6-methoxy-quinolin-4-yl] carboxylate (8.3 g; 0.038 mol) and methyl [1-*tert*-butyloxycarbonyl)-3-(R)-ethenyl-piperidin-4-(S)-yl]-acetate (prepared from the reaction of Example 51b with diazomethane in ether) (8.5 g; 0.03 mol) in dry toluene (15 ml) under argon and the mixture was heated at 120 °C (oil bath) with stirring for 3 days. The cooled product was treated with aqueous ammonium chloride and extracted with dichloromethane (4 x 100 ml). The organic fraction was washed with water, dried over anhydrous sodium sulphate, and evaporated to dryness *in vacuo* to afford a brown oil that was chromatographed on a Biotage silica column (90 g) eluting with 10% - 30% ethyl acetate in hexane. The first product collected was [3R,4R]-1-(t-Butoxycarbonyl)-3-ethenyl-4-[1-(R,S)-methoxycarbonyl-2-oxo-2-(6-methoxyquinolin-4-yl)ethyl]piperidine (3.0 g). Found: EI MH^+ 469. $C_{26}H_{32}N_2O6$ requires M 468.

Further elution afforded [3R,4R]-1-methoxycarbonyl-3-ethenyl-4-[1-(R,S)-methoxycarbonyl-2-oxo-2-(6-methoxyquinolin-4-yl)ethyl]piperidine (3.0 g). Found: EI MH^+ 427. $C_{23}H_{26}N_2O6$ requires M, 426

(b) [3R,4S]-3-Ethenyl-4-[2-oxo-2-(6-methoxyquinolin-4-yl)ethyl]piperidine dihydrochloride

Method A

A solution of [3R,4R]-1-(t-Butoxycarbonyl)-3-ethenyl-4-[1-(R,S)-methoxycarbonyl-2-oxo-2-(6-methoxyquinolin-4-yl)ethyl]piperidine (Example 60a, 2.9 g) in tetrahdrofuran (50 ml) and 2M hydrochloric acid (200 ml) was heated under reflux for 4.5 hours and evaporated to dryness *in vacuo*. The residue was azeotroped with dry toluene (x 2) to afford the title compound as a hygroscopic foam (2.24 g).

Method B

A solution of [3R,4R]-1-methoxycarbonyl-3-ethenyl-4-[1-(R,S)-methoxycarbonyl-2-oxo-2-(6-methoxyquinolin-4-yl)ethyl]piperidine(Example 60a, 3.0 g) in 5M hydrochloric acid (100 ml) was heated under reflux for 18 hours. The product was

evaporated to dryness *in vacuo*, basified with 2N sodium hydroxide solution, and extracted with toluene (3 x 100 ml). The organic fraction was washed with brine, dried with anhydrous sodium sulphate and evaporated to dryness to afford the title compound (1.96 g) as the oily free base.

δ^1H ($CDCl_3$) 8.85 (d, *J* 4Hz 1H), 8.03 (d, *J* 8Hz, 1H), 7.75 (d, *J* 2 Hz 1H), 7.55 (d, *J* 4Hz, 1H), 7.40 (dd, *J* 8,2 Hz, 1H), 6.15 (m, 1H), 5.10 (m, 2H), 3.95 (s, 3H), 2.30 - 3.20 (m,), 1.60 (m, 3H). Found: EI MH^+ 311. $C_{19}H_{22}N_2O_2$ requires M 310.

(c) [3R,4S]-3-Ethenyl-1-heptyl-4-[2-oxo-2-(6-methoxyquinolin-4-yl)ethyl]piperidine

Example 60b (1.4 g; 3.68 mmol) was alkylated as described in Example 3. The product was chromatographed on a Biotage silica column (90 g) eluting with ethyl acetate-hexane (1:1) to afford the title compound (1.33 g; 88.5 %).

δ^1H ($CDCl_3$) 8.85 (d, *J* 4Hz 1H), 8.03 (d, *J* 8Hz, 1H), 7.75 (d, *J* 2 Hz 1H), 7.56 (d, *J* 4Hz, 1H), 7.41 (dd, *J* 8,2 Hz, 1H), 6.17 (m, 1H), 5.10 (m, 2H), 3.94 (s, 3H), 2.10 - 3.15 (m), 1.20 - 1.80 (m), 0.88 (t, *J* 6 Hz, 3H). Found: EI MH^+ 409. $C_{26}H_{36}N_2O_2$ requires MH, 409.

(d) Title compound.

Example 60c was reduced as described in Example 2 to afford an oil (0.21 g) containing the title compound as a 1:1 mixture of diastereomers.

δ^1H ($CDCl_3$) 8.85 (d, *J* 4Hz 1H), 8.03 (d, *J* 8Hz, 1H), 7.75 (d, *J* 2 Hz 1H), 7.56 (d, *J* 4Hz, 1H), 7.41 (dd, *J* 8,2 Hz, 1H), 6.17 (m, 1H), 5.10 (m, 2H), 3.94 (s, 3H), 2.10 - 3.15 (m), 1.20 - 1.80 (m), 0.88 (t, *J* 6 Hz, 3H). Found: EI MH^+ 411. $C_{26}H_{38}N_2O_2$ requires MH, 411.

Example 61 [3R,4R]-3-Ethenyl-1-heptyl-4-[2-(6-methoxyquinolin-4-yl)ethyl]piperidine

Example 60c (0.30 g) was reduced as described in Example 12a to afford the title compound (0.030 g) as an oil.

δ^1H ($CDCl_3$) 8.64 (d, *J* 4Hz 1H), 8.00 (d, *J* 8Hz, 1H), 7.35 (dd, *J* 8,2 Hz, 1H), 7.15 (m, 2H), 6.17 (m, 1H), 5.10 (m, 2H), 3.94 (s, 3H), 2.00 - 3.15 (m), 1.20 - 1.80 (m), 0.88 (t, *J* 6 Hz, 3H). Found: EI MH^+ 395. $C_{26}H_{38}N_2O_2$ requires M 394.

Example 62 [3R,4R]-3-Ethyl-1-heptyl-4-[2-(6-methoxyquinolin-4-yl)ethyl]piperidine.

(a) [3R,4R]-3-Ethyl-4-[2-(6-methoxyquinolin-4-yl)ethyl]piperidine.

Example 60b (0.30 g) was reduced as described in Example 12a for 16h. The product was chromatographed on a Biotage silica gel column (40 g) eluting with ethanol-

dichloromethane-35% ammonia (10:80:1) to afford firstly Example 61 then the title compound (0.089 g) as an oil.
δ^1H ($CDCl_3$) 8.65 (d, *J* 4Hz 1H), 8.01 (d, *J* 8Hz, 1H), 7.35 (dd, *J* 8,2 Hz, 1H), 7.20 (m, 2H), 3.94 (s, 3H), 2.50 - 3.10 (m), 1.20 - 1.85 (m), 0.91 (t, *J* 7 Hz, 3H). Found: EI MH^+ 299. $C_{19}H_{26}N_2O$ requires M 298

(b) [3R,4R]-3-Ethyl-1-heptyl-4-[2-(6-methoxyquinolin-4-yl)ethyl]piperidine.

Example 62a was alkylated as described in Example 3. The product was chromatographed on a Sep Pak silica column (10 g) eluting with ethyl acetate-hexane (1:1) to afford the title compound (0.083 g).
δ^1H ($CDCl_3$) 8.68 (d, *J* 4Hz 1H), 8.03 (d, *J* 8Hz, 1H), 7.35 (dd, *J* 8,2 Hz, 1H), 7.15 (m, 2H), 3.95 (s, 3H), 2.10 - 3.15 (m), 1.20 - 1.80 (m), 0.89 (m, 6H). Found: EI MH^+ 397. $C_{26}H_{40}N_2O_2$ requires M 396.

Example 63. 1-Heptyl-4-[2(*R,S*)-hydroxy-2-(6-methoxy-4-quinolinyl)ethyl]-piperidine

(a) 4-[2(*R,S*)-hydroxy-2-(6-methoxy-4-quinolinyl)ethyl]piperidine

The title compound was prepared by the addition of sodium borohydride to a solution of 4-[2-(6-methoxy-4-quinolinyl)-2-oxo-ethyl]piperidine [EP 31753A1] in *iso*propanol as described for Example 2.

(b) Title compound

A suspension of Example 63a (314mg, 1mmol), potassium carbonate (552mg, 4mmol) and 1-bromoheptane (0.18ml, 1.15mmol) in dry DMF (10ml)was heated to 80°C under an argon atmosphere for 3h. The reaction mixture was then partitioned between ethyl acetate and water and the organic layer washed four times with water. The organic layer was dried (magnesium sulphate) and concentrated to afford a brown oil (336mg). The crude material was purified by silica chromatography eluting with a 90:9:1 mixture of dichloromethane:methanol:0.88 ammonia to afford the *title* compound (258mg, 63%) which was then crystallised from ethyl acetate: MS (electrospray) 385MH^+; NMR ($CDCl_3$) 8.73 (1H, d, J 4.5Hz), 8.02 (1H, d, J 9.1Hz), 7.53 (1H, d, J 4.5Hz), 7.36 (1H, dd, J 9.2, 2.7Hz), 7.18 (1H, d, 2.7Hz), 5.47 (1H, m), 3.92 (3H, s), 2.97 (2H, m), 2.30 (2H, m), 2.08-1.89 (3H, m), 1.75 (4H, m), 1.6-1.2 (12H, m), 0.87 (3H, t, J 6.4Hz).

Example 64. [3S,4R]-3-Ethenyl-1-heptyl-4-[2-(6-methoxyquinolin-4-yl)ethyl]piperidine.

(a) [3S,4R]-3-Ethenyl-4-[2-(6-methoxyquinolin-4-yl)ethyl]piperidine.

A solution of Example 61 (0.14 g) in water (1.0 ml) was epimerised as described in Example 29. The product was chromatographed on a Sep Pak silica gel column (10 g) eluting with ethanol-dichloromethane -35% ammonia (10:80:1) to afford the title compound (0.065 g) as an oil.

δ^1H ($CDCl_3$) 5.50 (m, 1H), 5.05 (m, 2H). Found: EI MH^+ 297. $C_{19}H_{24}N_2O$ requires MH, 297.

(b) Title compound.

Example 64a was alkylated as described in Example 3 to afford the title compound (0.017 g) as an oil.

δ^1H ($CDCl_3$) 8.65 (d, *J* 4Hz 1H), 7.95 (d, *J* 8Hz, 1H), 7.35 (dd, *J* 8,2 Hz, 1H), 7.18 (m, 2H), 5.58 (m, 1H), 5.07 (m, 2H), 3.93 (s, 3H), 2.80 - 3.15 (m), 1.20 - 2.35 (m), 0.88 (t, *J* 6 Hz, 3H). Found: EI MH^+ 395. $C_{26}H_{38}N_2O_2$ requires M 394.

Example 65 N-(6-Methoxy-4-quinolinyl)-1-heptyl-4-piperidinecarboxamide

Example 53a (375mg, 1.47 mmol) in THF (10ml) containing aqueous sodium hydroxide was heated under reflux for 2 hours. After cooling the solution was acidified with conc.HCl and the solvent evaporated. The residue was suspended in dichloromethane (10ml), then oxalylchloride (0.39ml, 4.4mmol) and DMF (1 drop) were added. The mixture was stirred at room temperature for 1 hour, and the solution was evaporated *in vacuo*. The solid was dissolved in dichloromethane (4ml) and added to a solution of 4-amino-6-methoxyquinoline (256mg, 1.47mmol) and 4-dimethylaminopyridine (359mg, 2.94mmol) in dichloromethane (10ml). The mixture was stirred at room temperature for 1h, and the solvent was evaporated *in vacuo*. The residue was dissolved in ethyl acetate and the solution washed with aqueous sodium bicarbonate. The organic layer was dried over magnesium sulphate and evaporated in vacuo. The crude product was purified by column chromatography eluting with 2 to 10% (9:1 methanol/ .880 ammonia)/dichloromethane to afford the title compound (110mg, 20%) as an off-white solid.

δ^1H ($CDCl_3$) 8.71 (1H, d, *J* 5.0 Hz), 8.17 (1H, d, *J* 5.0 Hz), 8.03 (1H, d, *J* 9.3 Hz), 7.83 (1H, br s), 7.39 (1H, dd, *J* 2.5, 9.3 Hz), 6.99 (1H, d, *J* 2.5 Hz), 3.96 (3H, s), 3.10-3.00 (2H, m), 2.56-1.22 (21H, m), 0.94-0.80 (3H, t, *J* 6.1)

MS (+ve ion electrospray) m/z 384 (MH+)

Example 66 (3*Z*)-(4*R*)-3-Ethylidene-1-heptyl-4-[3-(6-methoxyquinolin-4-yl)propyl]piperidine.

(a) (3*Z*)-(4*R*)-3-Ethylidene-4-[3-(6-hydroxyquinolin-4-yl)propyl]piperidine

Lithium ribbon (2.8g, 400mmol) was dissolved in dry THF (100ml) containing triphenylphosphine (20g, 76mmol) and the mixture stirred at room temperature for 6 hours.

Example 26a (5.0g, 16.1mmol) was dissolved in dry THF (50ml) and 22.5ml of a 1.04M solution of diphenylphosphine in benzene was added, followed by 60ml of the deep red solution resulting from the reaction of lithium ribbon with triphenylphosphine.

The resulting mixture was heated at reflux under argon for 60 hours. After cooling, the reaction was diluted with chloroform (230ml) and water (120ml). The pH of the mixture was adjusted to 9 by the addition of concentrated hydrochloric acid. After separating, the organic phase was washed with brine, dried over magnesium sulphate and concentrated *in vacuo*. The product was partially purified by chromatography on silica gel eluting with 80:18:2 chloroform/ ethanol/35% ammonia solution to give partially pure title compound (838mg).

δ ^{1}H ($CDCl_3$) *inter alia* 5.18 (1H, q, *J* 6.7Hz), 1.60 (3H, d, *J* 6.7Hz). MS (-ve ion electrospray) m/z 295 $[M-H]^-$.

(b) (3*Z*)-(4*R*)-3-Ethylidene-1-heptyl-4-[3-(6-hydroxyquinolin-4-yl)propyl]piperidine

Partially purified Example 66a was alkylated as described in Example 22b. The product was purified by chromatography on silica gel eluting with 95:4.5:0.5 chloroform/ ethanol/35% ammonia solution to give the title compound (112mg).

δ ^{1}H ($CDCl_3$) 8.60 (1H, d, *J* 4.4Hz), 7.98 (1H, d, *J* 9.0Hz), 7.32 (1H, dd, *J* 9.0, 2.6Hz), 7.27 (1H, d, *J* 2.6Hz), 7.13 (1H, d, *J* 4.4Hz), 5.25 (1H, br s, exch), 5.17 (1H, q, *J* 6.7Hz), 3.25 (1H, d, *J* 12.2Hz), 2.94-2.70 (4H, m), 2.47-2.39 (2H, m), 2.00 (1H, m), 1.79 (1H, m), 1.71-1.52 (5H, m) 1.61 (3H, d, *J* 6.7Hz),1.40-1.21 (11H, m), 0.85 (3H, t, *J* 7.0Hz). MS (+ve ion electrospray) m/z 395 (MH^+).

(c) Title compound

(3*Z*)-(4*R*)-3-Ethylidene-1-heptyl-4-[3-(6-hydroxyquinolin-4-yl)propyl]piperidine (49mg, 0.12mmol) was dissolved in methanol:acetonitrile (1:9, 6ml). *N,N*-Diisopropylethylamine (22ul, 0.12mmol) was added, followed by trimethylsilyldiazomethane (62ul, 0.12mmol). The reaction mixture was stirred for 18 hours at room temperature and then concentrated *in vacuo*. The product was purified by chromatography on silica gel eluting with 95:4.5:0.5 chloroform/ ethanol/35% ammonia solution to give the title compound (10mg, 20%).

δH ($CDCl_3$) 8.67 (1H, d, *J* 4.4Hz), 8.00 (1H, d, *J* 9.0Hz), 7.37 (1H, dd, *J* 9.0, 2.6Hz), 7.22 (1H, d, *J* 2.6Hz), 7.20 (1H, d, *J* 4.4Hz), 5.26 (1H, q, *J* 6.7Hz), 3.96 (3H, s), 3.16-2.99 (3H, m), 2.79 (2H, m), 2.45-2.32 (3H, m), 2.05 (1H, m), 1.92-1.23 (16H, m), 1.65 (3H, d, *J* 6.7Hz), 0.88 (3H, t, *J* 6.8Hz). MS (+ve ion electrospray) m/z 409 (MH^+).

Example 67. [3R,4S] -1-Cinnamyl-4-[2-(6-methoxyquinolin-4-yl)-oxyethyl]piperidine.

(a) 6-Methoxy-4-chloroquinoline.

To $POCl_3$ (5 ml, 53.7 mmol) cooled in ice 6-methoxyquinoline N-oxide (1 g, 5.7 mmol) was added in portions. After addition the mixture was refluxed gently for 30 mins. The cooled mixture was poured with stirring to crushed ice (25 g). Successive partial neutralisations with conc. aq. ammonia precipitated first the 2-chloro derivative and then the 4-chloro derivative. The 6-methoxy-4-chloroquinoline was partitioned between water and ethyl acetate, the combined organic extracts were dried over $NaSO_4$ and concentrated in *vacuo*. Yield, 0.31 g, 28%.

MS. : m/z 193/195 $(M+H)^+$

(b) [3R,4S] -1-t-Butoxycarbonyl-4-[2-(6-methoxyquinolin-4-yl)-oxyethyl]piperidine.

To a solution of 2-(1-t-butoxycarbonyloxypiperidin-4-yl) ethanol (0.1 g, 0.44 mmol) in dry DMSO (0.5 ml), sodium metal (0.01 g, 0.44 mmol) was added under argon and left to stir for 1 hour. After 1 hour Example 67a (0.08 g, 0.44 mmol) was added and microwaved for successive 2 minute 'bursts' at 50W. After 8 mins the mixture was allowed to cool and was poured into water (50 ml). The mixture was then extracted with ether (3x50 ml). The organic extracts were then combined and dried over $NaSO_4$ and concentrated under vacuum. The crude product was purified by column chromatography on silica gel 60, pre-absorbing onto silica and eluting with 0-30% EtOAc/Hexane. Yield, 0.07 g.

MS. : m/z 386 $(M+H)^+$

(c) [3R,4S]-4-[2-(6-methoxyquinolin-4-yl)-oxyethyl]piperidine

Example 67b (0.065 g, 0.17 mmol) was dissolved in DCM (10 ml), TFA (5 ml) was added dropwise over ~15-20mins, with stirring at 0°C. After stirring O/N saturated potassium bicarbonate solution was added until pH~9. The solution was then extracted with DCM (3x100 ml), washed with brine (100 ml), dried over $NaSO_4$ and then concentrated under vacuum. Yield, 0.322 g, 65%.

MS. : m/z 286 $(M+H)^+$

(d) Title compound

REM resin [1.2 mmol/g] (0.664 g, 0.79 mmol), and Example 67c (0.251 g, 0.88 mmol) were suspended in dry DMF (8 ml) and agitated on a rotator for ~96 hours. The resin was then washed with DMF (3x15 ml), DCM (3x15 ml), 3:1 DCM/MeOH (15 ml), 1:1 DCM/MeOH (15 ml), 1:3 DCM/MeOH (15 ml), MeOH (3x15 ml) and then left O/N under high vac.

This resin was suspended in dry DMF (10 ml), cinnamyl bromide (1 ml, 6.7 mmol) was added. This was then agitated on a rotator for 24 hours. The resin was then washed with DMF (10 ml), DCM (10 ml), 3:1 DCM/MeOH (10 ml), 1:1 DCM/MeOH (10 ml), 1:3 DCM/MeOH (10 ml), MeOH (2x10 ml) and then left O/N under high vac.

This resin was then suspended in dry DCM (5 ml) and triethylamine (1.5 ml, 11 mmol) was added. The solution was then agitated on a rotator at room temp O/N. The resin was then washed with DCM (3x10 ml). The washings were combined and poured into saturated KCO_3 (30 ml) and extracted with ethyl acetate (3x30 ml), dried and then concentrated under vacuum. The crude product was purified by column chromatography (CH2Cl2:MeOH:NH3; 9:1:0.1) to give the title compound (0.016 g).

^1H NMR ($CDCl_3$) : 1.64 (4H, m); 1.85 (1H, d, J = 12.8Hz); 1.94 (2H, q, J = 6.4Hz); 2.05 (2H, m); 3.08 (2H, m); 3.22 (2H, m); 3.92 (3H, s); 4.25 (2H, t, J = 6.4Hz); 6.33 (1H, m); 6.53 (1H,); 6.69 (1H, d, J = 5.2Hz); 7.30 (4H, m); 7.44 (1H, d, J = 2.8Hz); 7.94 (1H, d, J = 9.3Hz); 8.60 (1H, d, J = 4.8Hz).

MS. : m/z 402 $(M+H)^+$

Example 68 [3R,4R]-3-(2-Acetoxyethyl)-1-heptyl-4-[3-(6-methoxy-quinolin-4-yl)propyl]piperidine

Example 31 (0.100g) was dissolved in dry pyridine (5 ml) and stirred at room temperature while acetic anhydride (132 ul) and 4-dimethylaminopyridine DMAP (catalytic amount) were added. The reaction mixture was stirred at room temperature for 60 hours. The mixture was diluted with ethyl acetate (50 ml), washed with water (3 x 20 ml), dried over anhydrous magnesium sulphate, filtered and evaporated. This gave the title compound (0.083g, 75%).

δH ($CDCl_3$) 1.98 (s, 3H)

EI MH^+ ,469. $C_{29}H_{44}N_2O_3$ requires MH, 469.

Example 69 [3R,4R]-3-Ethyl-1-heptyl-4-[3-(6-{2-hydroxyethyloxy}quinolin-4-yl)propyl]piperidine

(a) [3R,4R]-3-Ethyl-1-heptyl-4-[3-(6-{tert-butyloxycarbonyl}methyloxyquinolin-4-yl)propyl]piperidine

The title compound (0.18g, 52%) was prepared from Example 22a using the general alkyation method of Example 23 and t-butylbromoacetate.

MS (+ve ion electrospray) m/z 511 (MH+)

(b) Title compound

Example 69a (0.18g, 0.00035 mole) was reduced as described in Example 26c. Column chromatography eluting with 2% (9:1 methanol/.880 ammonia)/dichloromethane afforded the title compound (0.09g, 58%) as a colourless gum.
MS (+ve ion electrospray) m/z 441 (MH+)

Example 70 [3R,4R]-3-(Ethylaminocarbonyloxyethyl)-1-heptyl-4-[3-(6-methoxyquinolin-4-yl)propyl]piperidine.

Example 31 (0.5g, 0.7mmol) was dissolved in toluene (2ml) and ethylisocyanate (0.06ml, 0.77mmol) added dropwise. After stirring at 50°C for 3 h, sat. sodium bicarbonate solution (50ml) was added and the products extracted with ethyl acetate. Drying, evaporation to dryness and column chromatography gave the product as aclear oil (0.323g, 67%).
E.I. MH^+, 498. $C_{37}H_{27}N_3O_3$ requires MH, 498.

Example 71 [3R,4R]-3-Ethenyl-1-heptyl-4-[3-(R,S)-aminocarbonylamino-3-(6-methoxyquinolin-4-yl)propyl]piperidine

Example 43 (0.250g) was dissolved in hydrochloric acid (0.2 ml of 5M and diluted to 10 ml) and THF (3 ml). Potassium cyanate (0.053g) was added and the reaction mixture heated at 100 °C for 50 minutes. Saturated sodium bicarbonate solution (40 ml) was added and the mixture extracted with ethyl acetate (2x50 ml). The combined organic extracts were dried over anhydrous magnesium sulphate, filtered and the solvent evaporated. Column chromatography on silica-gel gave the title compound as a cream coloured gel (0.076g, 28%).
E.I. MH^+ 467. $C_{28}H_{42}N_4O_2$ requires MH, 467.

Example 72 [3R,4R]-3-Ethyl-1-heptyl-4-[3-(6-(4-aminobutyloxy)-quinolin-4-yl)propyl]piperidine.

The title compound was prepared from Example 14 and *N*-5-bromobutylphthalimide by an analogous process to those described in Examples 16 and 17.
E.I. MH^+, 468. $C_{30}H_{49}N_3O$ requires MH, 468.

Table 1

The following compounds of the prior art are prepared by processes analogous to those described in the Examples

Table 2

The following novel compounds were prepared by processes analogous to those described in the Examples

Table 1

(n=1)

Compound no.	R^1 (6-position)	R^2	R^3	R^4	A-B
73	hydroxy	H	ethyl	n-nonyl	CH_2CH_2
74	methoxy	H	ethyl	3-(4-fluorobenzoyl)-propyl	CH_2CH_2
75	methoxy	H	ethyl	n-pentyl	CH_2CH_2
76	methoxy	H	ethyl	3-methylbutyl	CH_2CH_2
77	methoxy	H	vinyl	3-benzoylpropyl	CH_2CH_2
78	methoxy	H	vinyl	n-pentyl	CH_2CH_2
79	methoxy	H	vinyl	3-(4-fluorobenzoyl)-propyl	CH_2CH_2
80	methoxy	H	vinyl	3-(4-fluorobenzoyl)-propyl	CHOH-CH_2
81	methoxy	H	ethyl	n-pentyl	CHOH-CH_2
82	methoxy	H	ethyl	4-methoxybutyl	CHOH-CH_2
83	methoxy	H	ethyl	4-benzoylbutyl	CHOH-CH_2
84	$(CH3)_2CH(CH_2)_2O$	H	ethyl	n-propyl	CHOH-CH_2
85	$(CH3)_2CH(CH_2)_2O$	H	ethyl	n-butyl	CHOH-CH_2
86	methoxy	H	vinyl		CH_2CH_2
87	methoxy	H	ethyl	n-heptyl	CH_2CH_2
88	methoxy	H	ethyl	4-benzoylpropyl	CHOH-CH_2
89	methoxy	H	ethyl	CH_2CH=CHPh	CH_2CH_2

Table 2

Compound no.	R^1 (6-position)	R^2	R^3	R^4	n	A-B
90	methoxy	H	H	n-heptyl	1	$CH_2CH(OAc)$
91	hydroxy	H	vinyl	n-heptyl	1	CH_2CH_2
92	methoxy	H	vinyl	pyridylmethyl	1	CH_2CH_2
93	methoxy	H	vinyl	cyclohexylmethyl	1	CH_2CH_2
94	methoxy	H	ethyl	ethyl	1	CH_2CH_2
95	methoxy	H	ethyl	i-butyl	1	CH_2CH_2
96	i-butoxy	H	ethyl	n-heptyl	1	CH_2CH_2
97	n-pentyloxy	H	ethyl	n-heptyl	1	CH_2CH_2
98	hydroxy	with R^3	$=CHCH_3$	n-heptyl	1	CH_2CH_2
99	methoxy	H	vinyl	n-heptyl	1	$C(=CH_2)CH_2$
100	methoxy	H	vinyl	n-heptyl	1	$C(=CHCO_2Me)CH_2$
101	methoxy	H	vinyl	n-heptyl	1	$C(OH)(CH_2CH=CH_2)CH_2$
102	methoxy	H	vinyl	n-heptyl	1	$CH(NHMs)CH_2$
103	methoxy	H	H	n-heptyl	1	$NHCH_2$
104	methoxy	H	H	$CH_2CH=CHPh$	1	CONH
105	methoxy	H	H	n-heptyl	1	NHCO
106	2-methyl	H	H	$CH_2CH=CHPh$	1	OCH_2
107	methoxy	H	vinyl	n-heptyl	1	SCH_2
108	methoxy	H	vinyl	n-heptyl	2	CONH
109	methoxy	H	vinyl	n-heptyl	2	CH_2O
110	methoxy	H	H	n-heptyl	2	OCH_2
111	methoxy	H	vinyl	n-heptyl	0	$COCH_2$
112	methoxy	H	ethyl	n-heptyl	0	SCH_2

Biological Activity

The MIC (μg/ml) of compounds E2 and 89 against various orgamisms was determined and compared with Vancomycin.

Example 2 was tested as a 1:1 mixture of its isomers about the CH(OH) unit and separately as isomer (I) and isomer (II).

Organism	Vancomycin	Example 2			Example 89
		(1:1)	(I)	(II)	
E. coli ESS	>64	4	8	2	8
Staph. aureus "south"	2	0.25	2	0.125	≤0.5
Staph. aureus V573	1	0.25	2	0.125	≤0.5
Staph. aureus Russell	2	0.5	2	0.125	≤0.5
Staph. epidermis 11047	2	2	4	1	2
B.subtilis 6633	0.5	64	>64	64	16
Strep. faecolis I	2	4	4	2	2

The following compounds showed an MIC of less than 100 μg/ml against certain of the organisms listed above:
E2, E3, E4, E5, E6, E7, E8, E9, E10, E11, E12, E13, E14, El5, E16, E17, E18, E19, E20, E21, and compounds 73-82 and 84-89 of Table 1.

Compounds E21 to E72 showed an MIC of less than or equal to 16μg/ml against one or more of a range of gram positive and gram negative bacteria.